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BACTERIAL WARFARE'

A CRITICAL ANALYSIS OF THE AVAILABLE AGENTS, THEIR POSSIBLE MILITARY APPLICATIONS, AND THE MEANS FOR PROTECTION AGAINST THEM

This review was prepared by the writers as private citizens during the months immediately after the entry of this country into the war. The authors had no access to confidential information; the paper, therefore, contains only data that were publicly available before 1942. It was treated as confidential during the war emergency and is now published by virtue of the removal of wartime restrictions. Publication of this compilation of data pertaining directly or indirectly to bacterial warfare seems desirable not only for the sake of its value per se, but also as a contribution to an informed discussion of the portentous moral and political issues involved.

As the authors became associated with the government's biological warfare prof qt, they are not in a position to incorporate into the review data published since 1942. Thus, it cannot be helped that certain portions of the paper are outdated by developments of recent years as, for instance, in the field of virus research. It wilt not escape the informed reader, that in a striking number of cases, technical developments discussed as possibilities in this paper have already, become realities as evidenced by recent publications.—Ed.

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The Properties of Infective Agents of Warfare. Comparison with Chemical Agents 12

This report, as submitted by the authors to the National Research Council on June 8, 1942, carried the following statement:

"This project was originally conceived by the writers as members of a subcommittee of the War Effort Committee of the American Association of Scientific Workers, New York Branch. An outline prepared by the subcommittee was submitted to Professor A. R. Dochez, who subsequently authorized the preparation of this report by the writers. The contents of this report, prepared for submission to Professor Dochez, are known only to the writers, and will not be divulged by them without due authorization."

This paper was withheld from publication during the war, and is now published in view of the removal of wartime restrictions. All statements of fact in this report are based on published literature. Opinions expressed are those of the authors as of the original date of submission, June 8, 1942. The paper is published herewith in its original form except that minor revisions have been made which in no way modify the sense of the original, and that the following matter included in the original has been deleted in order to conserve space : *a* note on the rise and fall of epidemics, prepared for the lay reader; a table giving data on agents preserved by the lyophile or analogous methods; and abstracts of papers on bacterial warf are.

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I. SUMMARY

This report is an attempt to evaluate the possibilities and the limitations of bacterial warfare on the basis of a study of the literature of the subject, and of pertinent data from the fields of bacteriology, epidemiology and public health. The survey indicates that the effective dissemination of disease agents in warfare is a distinct possibility, although direct experimental data are needed to permit one to predict the results of attempts at such dissemination.

Potential infective agents of warfare were selected, and their suitability for military use estimated, by reference to a series of predetermined criteria, namely, infectivity, casualty effectiveness, availability and resistance of the agent, means of transmission, epidemicity, availability of means of immunization and therapy, ease of detection and possible retroactivity. On the basis of these criteria 37 agents were eliminated because their properties indicated that they would be unsuitable for bacterial warfare. Thirty-three other disease agents were selected for detailed consideration. The selected group consists chiefly of bacterial and virus agents affecting man and animals. In addition several agents of diseases of plants are discussed. The agents of human disease, which are considered in greatest detail, include those transmitted by the water-borne, air-borne and vector-borne routes. Agents of some of the most common diseases are included, such as measles and influenza, as well as of less common diseases such as tularemia and psittacosis and of rare diseases such as melioidosis.

From the detailed study of these agents an attempt is made to derive certain principles applicable to bacterial warfare. Air-borne and vector-borne disease agents are considered to be of greatest potential usefulness because of the comparative ease with which they can be disseminated and the relative impotence of standard sanitary measures against them. The means of offense in bacterial warfare are analyzed in terms of prOduction and assembly of agents and methods

for their dissemination, the last to be carried out chiefly by means of airvaft. In addition, the properties of the disease agents are considered to fit them, within limitations which are mentioned, for the following military purposes: for the reduction of isolated strongholds or the siege of cities; for the disorganization of industrial areas behind the lines or of army centers and camps; for use as part of a "scorched earth" policy, and against valuable animals, food plants and industrial crops; and perhaps for more limited use in connection with close fighting and rapid movement. Finally, the means of defense against bacterial warfare are treated with respect to anticipation and warning against bacterial attack, detection of the infective agent, decontamination of terrain, and protection and control by other measures of sanitation and public health.

II. INTRODUCTION

The data presented in this report strongly suggest that bacterial warfare is feasible. Actual demonstration of its practicability is lacking, but there seems little doubt that among the agents whose properties are discussed, some are capable of accomplishing certain limited military objectives if they are used judiciously and with due recognition of their characteristics. The need for intensive study of this subject needs no other substantiation. This report is intended as a contribution toward such intensive study.

The writers are aware of the international conventions which prohibit bacterial warfare, and are impressed with the virtually unanimous unbelief in their effectiveness, expressed or implied by writers on the subject. These conventions have been reviewed by Fox (1933[2]), LeRenard (1936) and at some length by LeBourdelles (1939), and need not be reconsidered here. It is considered a military axiom that any weapon is judged useful if it can be expected to accomplish a military purpose, that is, the destruction or immobilization of men or of essential productive and military equipment and materials, without excessive risk to the user.

It is alleged that bacterial warfare has been used, both in the first and second World Wars. Rochaix (1936) in particular speaks of the earlier incidents, as well as of such analogous practices as the early attempts of Pasteur and Loir to destroy rabbits with the fowl cholera bacillus. Among the references appended to this report are those of Wickham Steed (1934) and of the recent allegation (Editorial, 1942) of the use of bacterial warfare by Japan in China during the present war. Only the last mentioned among all such reports seen by the writers is convincing in its details; and none of them, including the last, seems more than a tentative or even amateurish performance.

It is not a purpose of this report to advocate the use of bacterial warfare. Indeed, if there is a way to insure against its use it will probably lie along the path indicated by Prime Minister Churchill in his speech of May 10, 1942:

> We are, ourselves, firmly resolved not to use this odious weapon [poison gas) unless it is used first by the Germans. Knowing our Hun, however, we have not neglected to make preparations on a formidable scale.
>
> I wish now to make it plain that we shall treat the unprovoked use of poison gas against our Russian ally exactly as if it were used against ourselves, and if we are satisfied that this new outrage has been committed by Hitler we will use our great and growing air superiority in the West to carry gas warfare on the largest possible scale far and wide against military objectives in Germany.
>
> It is thus for Hitler to choose whether he wishes to add this additional horror to aerial warfare.

The likelihood that bacterial warfare will be used against us will surely be increased if an enemy suspects that we are unprepared to meet it and to return blow for blow. Moreover the public has heard vaguely of bacterial warfare and has not been altogether reassured by several popular tracts which have made light of it. Morale will be sustained on this point only by an assurance such as that of Mr. Churchill, that we know all about it and are well prepared with both defensive and offensive means.

It seems self-evident that adequate knowledge of the possibilities of bactetial warfare demands investigation of both the offensive and the defensive aspects of the subject. Effective defenses cannot be erected without an understanding of the weapons against which they are meant to protect, and of the means by which those weapons are to be used.

It is the purpose of this report, then, to describe the agents whose properties suggest their potential applicability in bacterial warfare; to indicate the principles which seem to govern their selection and application; to outline the methods by which they aright be used in warfare, and the classes of military objectives for which they appear suitable; to suggest the means that are available or should be made so for protection against them; and to point out some of the problems that require further investigation. This order of presentation has not been followed precisely for reasons of clarity. In particular, the discussion of individual agents in detail, constituting the bulk of this report and the basic data upon which the report depends, has been put near the end, preceded by consideration of the general principles of the subject.'

The term "bacterial" warfare is used as a convenient rather than an accurate designation of the field surveyed. Not only are bacteria and their products considered, but all other microscopic and submicroscopic agents of infection as well. This field is a broad one, and potentially useful agents may have been overlooked. To facilitate selection and consideration of such agents by others, lists are given in section IV of the agents rejected, with reasons for doing so, as well as of the agents selected for consideration.

The methods used in gathering and assembling the data and in deriving principles from them may be of interest. The general scope of the problem was first outlined from a study of the available literature on bacterial warfare as such. A set of general criteria was then drawn up to serve as a basis both for selection and for study of individual agents. The field was then surveyed for agents which seemed to meet the necessary criteria, and each of these agents was then studied in detail, using the larger current texts and the more recent literature. With these data available the remainder of this report was then prepared. The principles of bacterial warfare as presented have thus not been derived *a priori* but have been based directly on the properties of the available agents.

Papers on bacterial warfare are listed in a separate bibliography in section VI.

It is recommended that the data on individual agents be checked by spec lists in appropriate fields. No effort has been spared to be accurate, but errors may have been made. It may be noted that the field surveyed is constantly growing and changing; and the analysis presented here may become obsolete within a short time. Much of the significant data in this report appeared during the last ten years. New methods of cultivation and immunization, and particularly new infectious agents themselves which may be isolated, are likely to modify many of the views expressed. Completion of experiments proposed in this report are bound to induce such modification.

III. THE PRINCIPLES OF BACTERIAL WARFARE

THE PROPERTIES OF INFECTIVE AGENTS OF WARFARE. COMPARISON WITH CHEMICAL AGENTS

The field upon which we may draw for agents of bacterial warfare is large and very varied. It includes agents of diseases of men, of useful animals, and of food crops and other commercially valuable plants. This report is concerned mainly with diseases of man, and only secondary attention has been given to diseases of the others, chiefly because of the limitations of training of the writers. The destruction of food materials may, however, be equally important from a military standpoint, and deserves additional consideration.

The most useful agents for warfare are to be found among the bacteria proper and the filterable viruses; but spirochetes, rickettsiae, pleuropneumonia organisms, fungi and protozoa also require consideration; and insects and other arthropods, which serve as vectors for some of the infective agents, must also be examined.

It is of interest to compare bacterial warfare with poison gas warfare. The two fields are similar in that they employ agents which may be diffused over a large area and thus exert their incapacitating effects on large numbers of individuals simultaneously. They have the psychological similarity that both may be more or less invisible and intangible, so that their action is to a degree insidious; and part of their expected effect is that of demoralization through terror of the mysterious or unknown.

In other respects there is an overlap in the range of properties of poisons and infective agents. Most of the former exert their effects at the instant of contact, and have little or no ability to persist in the attacked area. Some, however, like mustard gas, have both a lag between contact and symptoms and a considerable degree of persistence. Infective agents, however, begin in these properties where poison gases end. All have a lag or *incubation period* intervening between contact and the first appearance of symptoms; this period is never less than a few hours and may last for many days.' All infective agents, moreover, manifest some degree of *persistence.* Of the agents which appear to be non-epidemic, some may prove to have even less persistence than mustard gas (e.g,, leptospiras), whereas others may nevertheless be expected to persist in certain types of terrain for long periods (e.g., tickborne agents).

Many infective agents (but not all) are characterized by a property not possessed by poison gases: that of *epidemicity,* or capacity to spread from one infected man (or animal or plant) to others, and thus to continue spreading over a more or less large area; so that a single effective attack, even though sharply localized at the source, may be potentially capable of spreading very widely. Another property which distinguishes infective agents from chemical poisons is *infectivity:* the frequency with which an infective agent induces symptoms in a random group of individuals. Infectivity is one of the primary criteria for selection of agents of bacterial warfare. A contributing factor which influences variation in infectivity *is immunity:* as a result of either natural or artificially instituted experience with the infective agent, some persons may become more or less resistant.

Infective agents differ from chemical poisons in other important respects which, like the foregoing, dictate essential differences in the means of their preparation and use and in the methods of protection against them. Infective agents are not manufactured or synthesized; they *proliferate,* and most of them may be prepared in unlimited amounts when supplied under suitable conditions with cheap and easily obtainable food materials. Yet infective agents are all highly complex and comparatively *unstable;* in particular, they are subject to attenuation or loss of virulence, or capacity to produce disease, especially when they are handled apart from the tissues of their characteristic human, animal or plant host. Another criterion for selection of infective agents has been based on this fact, and only such agents have been dealt with as are capable of being handled without loss of virulence. On the other hand virulence can often be enhanced.

It may be emphasized that all agents selected for consideration in this report are *dangerous* to handle. Many of the agents have been selected in part because of the known occurrence of infections among laboratory workers. The potentially useful agents of warfare thus include the most notorious offenders in this respect. They require handling under more than ordinary precautions, and by persons with more than ordinary skill. Fully adequate precaution and skill are however by no means inaccessible. In a similar sense, infective agents, used as weapons of warfare, are likely to be *retroactive.* That is, by virtue of their other properties, particularly their infectivity, their persistence and their epidemicity, they are capable in varying degree of affecting those using them as well as those against whom they are used. This property is not unknown in chemical warfare; but it may be much more pronounced with some of the infective agents. It is considered at length below; and, as will be seen, retroactivity is definitely not an insuperable obstacle to bacterial warfare.

THE DISSEMINATION AND SPREAD OF INFECTION IN GENERAL. EPIDEMIOLOGY IN PUBLIC HEALTH AND IN BACTERIAL WARFARE

The subject of epidemiology—the principles of infection as it occurs and spreads among populations—is a fundamental aspect of bacterial warfare. The

Some infective agents, like those of leprosy and rabies, have protracted incubation periods which may extend for weeks, months or even years ; and for this reason among others such agents have been rejected as unsuitable for bacterial warfare.

essence of bacterial warfare is the provocation of mass infections, and the achievement of this purpose demands as much knowledge as possible of the genesis of mass infections under natural conditions. Nevertheless it is important to emphasize that the contribution which natural epidemiology can make to bacterial warfare, however important, is severely limited, in that bacterial warfare is not natural but artificial.

Epidemiology as a branch of public health knowledge and practice studies the chain or cycle of events by which each disease is disseminated with the particular purpose of finding one or more vulnerable links in the chain which may be broken to interrupt the continuity of the disease. Vulnerable links are found in different parts of the chain for different diseases. With the typhoid group of fevers the weakest links found at the point where sewage pollutes drinking water. With syphilis it is the individual patient with active disease. With epidemic yellow fever it is the breeding places of Aedes aegypti mosquitoes; with sylvatic yellow fever, on the other hand, it is the point at which the virus enters man. For the student of bacterial warfare the emphasis shifts fundamentally. He is concerned with weak 1 nks only in order to strengthen them, or to discard the whole chain if they cannot be strengthened. He is much more interested in the inception of mass infections than he is in the details of their perpetuation, except, of course, that for purposes of defense against bacterial warfare, or for control of mass infections once they have begun, he must fall back on knowledge of the whole epidemiological chain.

Yet even from the defensive standpoint there is an important difference in emphasis between bacterial warfare and epidemiology of natural infections. Public health in any given area is concerned with diseases which are important problems in that area, and with those known to be capable of introduction into the area, and hence potentially important. It is not concerned with diseases which under natural conditions are not likely to be introduced into the area, however important they may be elsewhere. In bacterial warfare it is likely that the absence of a disease in a particular area will be considered an excellent reason for employing it in an attack on that area. In short, the worker in bacterial warfare must know the foreign diseases as well as the native ones.

Bacterial warfare differs from epidemiology in one additional respect which may be more important than any of those already mentioned. In considering the means of transmission of agents of bacterial warfare in a later section (IV), the writers searched for indications of means *other than* those known or believed to operate under natural conditions. Accidental infections of laboratory workers have furnished several such indications, of which a good example is the ability of yellow fever virus to infect man without the intermediation of the mosquito, perhaps by the air-borne route. This fact has no importance whatever in public health. Yellow fever virus is never present in the air or elsewhere in the environment apart from mosquitoes, in such a way as to infect man, except in laboratories where the virus is being grown and studied. Yellow fever is consequently never transferred in nature except by mosquitoes. But for purposes 'of bacterial warfare the observation that yellow fever virus can be transmitted apart from mosquitoes is of enormous potential significance. In the first place, the virus can be more conveniently handled without the vector; secondly, elimination of the mosquito portion of the transmission chain may make it possible to eliminate the exacting climatic requirements for the spread of yellow fever (which ordinarily depend on the mosquito); and thirdly, the mosquito happens to be the vulnerable link in the yellow fever chain (page 70). In other words, an observation recorded in 1931 (12) and apparently never followed up because it has no public health importance may turn out to be crucial in determining whether or not yellow fever virus is applicable as an agent of bacterial warfare.

THE TRANSMISSION OF DISEASE WITH SPECIAL REFERENCE TO BACTERIAL WARFARE

Infectious diseases may be conveniently classified into five broad groups on the basis of their route or pathway of infection. These are (A) the food-And water-borne group; (B) the contact group; (C) the air-borne group; (D) the vector-borne group; and (E) the endogenous group. The last, including diseases such as subacute bacterial endocarditis due to *Streptococcus viridans,* Vincent's angina and related diseases (218), and actinomycosis (43, 244), may be considered such that transmission of the infective agent through the environment is of no importance in their inception, which depends heavily on predisposing causes in the host. This last group is therefore of no consequence to bacterial Warfare, and will not be considered further. All the others, however, require analysis; and each may be further subdivided. Like all biological classifications this one is a matter of convenience only, and should not be considered absolute. The groups merge and overlap, and individual diseases must in many instances be placed in several groups.

The Food- and Water-Borne Group

This group may be divided into (a) the ingestion diseases, in which the infective agent enters the body selectively through the alimentary tract; and (b) the water-contact diseases, in which other routes of infection operate.

The Ingestion Diseases. The great water-borne epidemic diseases, cholera and typhoid fever, are characteristic of this group. Although other means of infection are known, the major source of large outbreaks in nature is the pollution of a drinking water supply with the intestinal contents of a case or carrier of the disease. When large numbers of persons drink such polluted water, as may occur in a city using a common water supply without sanitary safeguards, the result may be an explosive epidemic. Many persons become infected simultaneously or within a very short interval. One of the best known instances is the cholera epidemic in Hamburg in 1892, in which 17,000 cases and nearly 9,000 deaths occurred within about two months. An instructive feature of this epidemic is the fact that the neighboring city of Altona remained virtually free from infection, despite close contiguity and a common source of water in the river Elbe. The boundary between the two cities is political rather than natural, running in some places down the middle of a street. Altona, however, filtered

its drinking water; Hamburg did not. The source of infection seems neVer to have been determined. It is of passing interest here that the water may have been contaminated by inoculation with cultures of the cholera vibrio emptied into the sewage system from laboratories in Hamburg in which cholera was being studied at the time (267).

Cholera and typhoid fever are often the first diseases thought of by the uninformed when bacterial warfare is mentioned. There are several reasons, however, for which these diseases and the related *Salmonella* (paratyphoid) infections may probably be dismissed as unsuitable for this purpose; although one cannot be altogether certain that their use may not be attempted.

There are peculiar uncertainties in the infectivity of the agents of these diseases. During the controversy over the etiology of cholera following the isolation of the vibrio by Koch in 1883, several investigators intentionally swallowed cultures; some of these became infected but many did not. In both cholera and typhoid fever the number of infecting organisms, the nature of the medium in which they are suspended, and ill-defined factors of resistance in the recipient are all thought to be important in determining infectivity. Moreover, moderately effective vaccination is widely employed against four of the agents here considered (cholera, typhoid and paratyphoid A and B).

But more important is the fact that modern sanitary safeguards applied to drinking water in cities and among armies have virtually eliminated this group of diseases in those areas, constituting one of the greatest triumphs of public health practice. Normal sanitary safeguards as applied to water, in other words, are specifically adapted to prevent epidemics of cholera and typhoid fever. There may be a question as to whether massive inoculation of reservoirs is capable of overriding these precautions. Another question concerns the fact that standard tests for water pollution are based on contamination with sewage, and hence look for the more abundant and easily identifiable but non-pathogenic colon bacillus, rather than for the pathogens, as an index of presumptive infectivity. If it should prove possible to override sanitary safeguards and to contaminate drinking water with massive doses of pure cultures of cholera vibrios, typhoid or paratyphoid bacilli, or even all of these combined, conventional water pollution tests would fail to disclose their presence.

Intermediate among the food and water-borne diseases, overlapping with the cholera-typhoid group, are dysentery, *Salmonella* enteritis, staphylococcal food poisoning, and botulism. Bacillary dysentery and botulism are considered in detail in section IV as potential agents of warfare. Amebic dysentery seems impracticable chiefly because of the difficulty of propagating the causative agent in sufficient quantity for the purpose. *Salmonella* and staphylococcal food poisoning may be considered briefly here.

Most species of the genus *Salmonella* are essentially pathogens of animals, particularly rodents, and are usually capable of producing only a transitory gastro-enteritis in man. As agents to be directed against man they are therefore of secondary importance in themselves; but they might be employed in combination with other ingestion agents. They might also be used against food animals, for their direct effect in reducing the meat supply, or with a view to causing secondary food poisoning in man.

Staphylococcal food poisoning in man, on the other hand, probably has no important relationship with animals. Foods, especially bakery products, are contaminated by human handlers who carry enterotoxic staphylococci in the upper respiratory tract. Again the disease in man is an acute but transient gastro-enteritis with a fatality near zero and brief incapacitation. Human carriers of cholera, typhoid and paratyphoid fevers, and also of amebic and bacillary dysenteries, may distribute more severe infections in much the same way.

All these agents can be water-borne as well as food-borne, and the water-borne route seems to be more important for purposes of bacterial warfare, since it is potentially capable of reaching and infecting larger numbers of individuals. For deliberate infection of food animals, contamination of pasturage from the air may also be a feasible means. The deliberate employment of carriers of the diseases seems comparatively unimportant. Such carriers, or others serving as secret agents or saboteurs, who distributed cultures of these organisms to contaminate food, could hardly provoke more than small scale outbreaks. In the same class would be agents attempting to contaminate food in factories during the course of processing (see botulism, section IV). Such possibilities must be kept in mind. They are not difficult to guard against by standard procedures of testing, sanitation and policing.

The Water-Contact Diseases. The most characteristic member of this group is Weil's disease or leptospirosis, which is dealt with in detail in section IV. Brucellosis and tularemia may also be included here, although evidence, presented later for both diseases, suggests that their most likely application as agents of warfare may be by the air-borne route.

The Contact Infections

Contact infections may again be subdivided into (a) the direct contact or venereal infections; and (b) the indirect contact and wound infections. Infectious diseases transmitted by the respiratory route are not included here, despite the fact that direct contact transmission of infected droplets by sneezing and coughing is undoubtedly part of their epidemiology. As indicated in the general discussion of air-borne infections (page 19), it seems particularly important from the standpoint of bacterial warfare to separate the respiratory group from the others.

The Venereal Diseases. The true venereal infections, which are transmitted almost exclusively by sexual contact, have four epidemiological characteristics in common, which determine their nature as mass infections. They occur naturally only in human beings; the causative agents are present on the surface of the genital tract at some time during the course of the disease; during at least a part of the infective period the disease is not sufficiently incapacitating to preelude sexual intercourse; and the causative agent is incapable of survival in the environment for periods long enough to permit their dissemination by indirect

contact. The last two circumstances virtually eliminate this group frota consideration in bacterial warfare. The statement of Fox (1933) is worth noting,

> . . . The soldier's danger from the venereal diseases will not come from the open, wartime enemy who loves him least, but from the money-loving or uniform-worshit, ladies who profess to love him most.

The Indirect Contact and Wound Infections. This is a large and heterogetteo, group of diseases with which it is difficult to deal systematically. It in elu, nearly all the important diseases due to fungi; certain infections with stalph lococci and hemolytic streptococci; diseases caused by spore-bearing bacteri anthrax, tetanus and the gas gangrene group; and infections caused by awbite, such as rabies and rat-bite fever. Infections which result from cootawith animals may also be included here, although such diseases (brucellosis tularemia, glanders, and melioidosis) are probably all capable of transmis,sion by other routes, as noted in section IV. Anthrax is also considered in dtetail in section IV. Staphylococci have been mentioned under the ingestion disease (page 17) and will be considered again, with hemolytic streptococci, under air-borne infections. The animal-bite infections may be dismissed from considera tion. Rabies, in addition to its evident requirement for deep parenteral administration, seems to have a low attack-rate, and may have a very prolonged incubation period. Rat-bite fever appears to have a dual etiology. The presumed agent of one form, *Spirillum minus,* is not cultivable. That of the other, *Streptobacillus moniliformis,* has not been sufficiently studied: but the known properties of both agents are not such as to suggest a capacity for deep inoculation—which they seem to require—except through animal bite, which itself is not amenable to military control.

The fungi and the pathogenic clostridia thus remain to be discussed.

The *fungi* can probably also be dismissed as potential agents of warfare (mepl against plants; see section IV), although the authors of this review do not feel competent to make this decision, and suggest that it be reviewed by mycologists Most pathogenic fungi are associated with diseases characterized by great cla•onicity without marked incapacitation. *Epidermophyton* and allied ringworm infections—"athlete's foot" and the like—are potentially if not actually serious military problems, but it seems unlikely that they could be introduced succes.fully where they are not already present. *Sporotrichum schenkii* may be considered here because of its peculiar capacity to infect plants and animals as well as man (136, 267). Distribution of the fungus over vegetation in an isolated tropical stronghold might conceivably have some nuisance value, but the disease in man has an incubation period of several weeks and is not usually incapacitating. Another possibility lies in the application of *Aspergillus* species and other fungi associated with pulmonary naycoses in man.

The *pathogenic clostridia,* being spore-formers, have resistance properties analogous to those of the anthrax bacillus, and might be considered for similar purposes. They lack the infectivity of anthrax, however, and would be suitable for use only when inoculated deeply into injured tissue. For this purpose they might be used to contaminate shrapnel and other weapons. It is possible that spores, particularly if desiccated, may resist the instantaneous high temperature and pressure of detonation. Duffour (1937) mentions this possibility as having been "proved"; but the writers know of no actual data on this question. On the other hand, shrapnel wounds and other war wounds are very likely to be infected with clostridia without deliberate contamination of weapons, and it may be doubted that such contamination could effect an improvement upon nature sufficient to justify the effort. Since effective vaccination against tetanus is now part of army routine, this member of the group may probably be eliminated. The possible use of a combination of spores of anthrax and one or more of the gas-gangrene clostridia as a projectile contaminant may be worth experimental study.

The Air-Borne Infections

This group includes the largest number and probably the most importaa potential infective agents of warfare. The following are considered in detail in section IV: pneumonic plague, influenza, measles and mumps, psittacosis, anthrax, several diseases of animals, and, included somewhat unconventionally and in several instances tentatively, on the basis of evidence given for each agent, tularemia, brucellosis, glanders, melioidosis, yellow fever, and Rift Valley fever.

The air-borne route of infection seems to be the most practicable for bacterial warfare, and the agents listed above constitute its chief potential arsenal. It is therefore necessary to consider the mechanism of air-borne infection closely, particularly because as a concept it is comparatively new and has not yet achieved universal acceptance.

After the classical experiments of Pasteur and Tyndall had shown that bacteria are associated with the dust of the air, and that dust particles large enough to be visible in the Tyndall beam settle out rapidly in an enclosed space, the view came to be accepted that bacteria do not remain long suspended in air. When Fltigge later showed that bacteria in droplets sneezed or coughed into the air could be recovered only at relatively short distances from their point of origin, he seemed to establish the idea that respiratory infections can be transmitted only by direct transfer of infected droplets. This concept of droplet infection as the sole means of transmission of most infections of respiratory origin was generally accepted until recently. Early observations that infection via the. respiratory tract with the organisms of ,plague, tuberculosis and anthrax may occur at a distance and independently of droplets have been regarded as exceptions; and the well-known ability of measles and chickenpox to spread rapidly in flagrant disregard of the droplet concept has been put down as baffling, but has not disturbed the theory.

A large and growing body of data developed chiefly during the last ten years indicates that droplet transfer by close contact is only an alternative means of transmission of infections of respiratory origin. Of apparently far greater epidemiological significance is their transmission at a distance in both space and time. The pioneer in developing these data seems to have been the French worker

Trillat, whose studies are cited in papers on bacterial warfare by his countrypea The most convincing findings, however, have been those of Wells and his collaborators, and of Buchbinder, Phelps and their co-workers in this country. Buellbinder (27) has recently reviewed this subject at length. The relevant facts seem to be these:

By the use of suitable apparatus for collecting air and concentrating the bacteria in it, such as the Wells air-centrifuge, it has been shown that bacteria sprayed into the air can be recovered from it for many hours afterward. In an experimental chamber, bacteria thus sprayed as a fine mist (or "artificially sneezed") into the air settle out at a rate of about 20 per cent per hour, so that appreciable numbers remain suspended after 24 hours. Moreover, significant numbers of bacteria (hemolytic streptococci) were sometimes found alive on the floor of the chamber several weeks after settling; and tests of mouse virulence and other pathogenic properties showed little or no impairment of their capacity to produc6 disease. In addition to hemolytic streptococci the following infective agents have been studied by this or analogous methods and have been found capable of inducing infection via the air at a distance from the source and after a lapse of time; pneumococci and vaccinia virus (27), influenza virus (295), poliomyelitis virus (76), and tubercle bacilli (297). So far as is known, no respiratory pathogen tested by such methods has thus far been found incapable of such air-borne transmission, but further experimental data are needed.

Clinical studies (27) on the epidemiology of infections occurring in hospitals with hemolytic streptococci, pneumococci and diptheria bacilli strongly suggest the great practical importance of the air-borne route of infection. An additional item of supporting evidence is the recent effective use of barriers of ultraviolet irradiation and of germicidal aerosol sprays to prevent the transmission of infective agents through the air.

The bearing of these findings on bacterial warfare is far-reaching. It may be said, in view of developments of recent years, that Fox was justified in doubting the feasibility of bacterial warfare in 1933, but that such justification no longer exists. The airplane makes possible the dissemination of infective agents far beyond the enemy lines; while the concept of air-borne infection indicates that such agents need not make immediate contact with individuals, but can survive in a virulent state after they settle, and after they have been raised again by air currents and by human movements.

The airplane is clearly the most useful means for the dissemination of infective agents, whether their own means of transmission be via the air, or whether it be by water, by contact, or by vectors. In the three latter instances the means of attack would consist chiefly in the deposition of the infective agent in the appropriate body of water or the selected terrain, or the liberation of the vector in a manner such that it may reach the ground safely. For air-borne infections proper, however, additional considerations are involved.

Dissemination of air-borne agents may not be a simple matter. It may not suffice merely to spray suitable agents in liquid suspension or in dry form over the area of attack. Under natural conditions infections of respiratory origin spread by predilection in cold weather; they undoubtedly spread most effectively

in closed spaces—indoors—where many individuals crowd together for appreciable periods of time. Buchbinder (28) has recently collected data which indicate that the most important areas where such infections become epidemic may be dormitories or barracks—large rooms in which many persons sleep close together. In such areas effective dissemination must depend on the accumulation of sufficient concentrations of the infective agent from one or more human sources. The required concentration should be more easily provided under artificial conditions. It may be, however, that artificial dissemination of airborne agents will not prove effective out of doors. It may be found necessary to incorporate such agents for dissemination from aircraft in heavier-than-air media analogous to chemical fogs and smoke screens; to deposit them from low-flying planes over habitations or factories under meteorological conditions such that the contaminated "smoke" may be expected to seep through crevices and through open windows and thus infect indoor environments. Such conditions, however, cannot be predetermined theoretically. Using the concept of air-born infection as a broad working hypothesis, suitable experiments on animal colonies in and out of habitations, in a prearranged environment with controlled temperature, humidity and wind direction and velocity, and perhaps with additional controls which the writers are not competent to suggest, seem alone to be capable of determining these conditions adequately. It is understood that such investigations are hardly possible under the usually limited facilities of university research, and, indeed, that they could hardly be undertaken at all except under the direct supervision of the War Department. They are entirely practicable, however; and incidentally, they may be expected to provide information of great value in public health epidemiology as well as in bacterial warfare.

In this connection it may be noted that a group of investigators supported by the Rockefeller Foundation have been conducting epidemiological experiments on tuberculosis in monkeys on a small uninhabited island near Jamaica. Investigations under similar conditions might also be useful for the present purpose.

Certain individual air-borne infections, not dealt with in section IV, require brief consideration here:

Respiratory Diseases. Pathogenic *staphylococci* and *streptococci* have not been dealt with in detail as potential agents of warfare because from their properties it appears that, by themselves, they are of doubtful suitability. Hemolytic streptococci certainly, and pathogenic staphylococci probably, are capable of air-borne transmission. Staphylococci produce an uncommon but pernicious pneumonia; streptococci commonly induce severe secondary broncho-pneumonia. Both microorganisms are associated in many of their most severe manifestations with other infective agents. It is in such mixtures, for example with influenza virus or measles virus (or both) that these agents may find their most important place in bacterial warfare. Much the same may be said for the *influenza bacillus,* which likewise deserves investigation as an agent in combination with others for air-borne bacterial warfare (see page 50).

The *pneumococcus* and *Friedlander's bacillus (Klebsiella pneumoniae)* are capable of inducing severe disease. Pneumococcal pneumonia seems in a restricted sense to be a communicable disease (27). Its high carrier rate during

the cold season seems to have little direct bearing on its epidemiology, the ,`normal" pneumococcus types being infrequently involved in frank disease (270)... On the other hand the occurrence of pneumonia depends on predisposing factors such as fatigue and antecedent respiratory infections due to other agents, and seems to have, at best, a low attack-rate. This fact may eliminate the pneumococcus from consideration here. Whether the pneumococcus or the bacillus of Friedlander can be used in combination with other air-borne agents can be determined only by experimentation. It may be worth noting that Christie (39) reported 60 cases of piaeumococcal pneumonia out of 90 pneumonic complications of influenza

The *diphtheria bacillus* and *Hemophilus pertussis* seem likewise of doubtful utility as agents of warfare. Their attack rate in adults in most communities seems to be low. More or less effective immunization is available for both, and is coming to be widely practiced.

Tuberculosis may be eliminated from serious consideration because of its great chronicity. The meningococcus and the common cold virus are considered in section IV (see also "new" agents, page 87).

Other Diseases of Respiratory Origin,. Except for measles and mumps, and certain other diseases which may be listed in this category and are discussed in section IV (e.g. tularemia), only three infections call for consideration 'here: *variola, varicella* and *rubella.* All three can be eliminated as agents of warfare, smallpox because of almost universal vaccination, chickenpox and German measles because, as far as is known, the agents have not been effectively cultivated and could therefore not be made available in adequate amounts.

The Vector-Borne Infections

Several agents of presumed potential importance in bacterial warfare are included under this head in section IV: the plasmodia of malaria, dengue virus, equine encephalomyelitis virus, tick-borne relapsing fever spirochetes, and the pathogenic rickettsiae. This group is probably second in importance to the air-borne agents. The natural group includes diseases caused by bacteria, spirochetes and viruses, all the rickettsial diseases, nearly all protozoan infections and many diseases caused by higher parasites. In the last two categories all but malaria have been eliminated chiefly on the ground that the causative agent cannot be made available in sufficient quantity. These will not be considered individually.

The vector-borne diseases constitute a varied group, and are subdivided on the basis of the particular vector concerned, since the environmental requirements and habits of the vector largely determine the epidemiological characteristics of the disease. The group thus comprises diseases transmitted by (a) fleas and lice, (b) mosquitoes, (a) ticks, and (d) other vectors.

The Flea- and Louse-borne Group. The diseases to be considered are bubonic plague and murine typhus' (flea-borne), and epidemic typhus, epidemic relapsing fever and trench fever (louse-borne). Murine typhus is somewhat distinct from the others; except in so far as it may be the initial phase of a louse-borne epidemic (166) it is a sporadic rather than an epidemic disease. The others are highly epidemic and may be considered together since the prevalence of either vector implies certain common environmental conditions: in particular, crowding with gross insanitation and lack of personal hygiene. These are diseases of poverty on the scale found in India, and of the social disorganization characteristic of wars and their immediate sequelae. Despite the fact that these diseases have a special predilection for armies, however, we regard them as unsuitable for bacterial warfare. If conditions are appropriate for their development they are likely to appear and spread without human intervention; and if such conditions are absent, nothing like the severe natural epidemics could be expected to result from, artificial introduction of the causative agent.

These diseases, except bubonic plague, can probably be eliminated for additional reasons: murine typhus, because its epidemiology is complex and does na seem well understood; louse-borne typhus and relapsing fever, because of difficulties in making the agent available in suitable quantity, in the vector or otherwise; and trench fever, because its causative agent is not definitely known. But the potential applicability of bubonic plague in warfare requhes qualification.

Like cholera and typhoid fever, bubonic plague seems an obvious possibility for bacterial warfare at first glance, but further consideration reveals the difficulties that would face an attempt to employ it. Beyond its dependence on social disorganization, bubonic plague is a disease with a complex epidemiological chain in which rats or other wild rodents and their fleas form intermediary links to man. Large epidemics are probably always initiated by migrating rodent carriers of plague bacilli from an endemic area in which the rodent population is largely immune to an area where new susceptible rodents are present. The result is an epizootic among the rodent population, which in one or more stages may be carried to man through the transference from dead rats to man of the rat flea. This insect, in the absence of considerable numbers of living rodents, then passes rapidly from man to man. This chain of events is made more complex by the rather exacting requirements of the flea for warm but not hot weather and a rather high relative humidity.

It follows that an attack using plague bacilli in infected fleas or rats, or with cultures intended to infect these species, could have little expectation of success unless the conditions of the terrain and environment were selected with minute care. There may be relatively few areas on the earth where plague conditions are present but plague itself is absent. The Japanese may have selected such areas in China for their alleged attempt to disseminate infected fleas (Editorial, 1942); yet their experiment, if it was such, did not prove remarkably successful. Favorable conditions may possibly exist in this country, expecially in the southeastern States; and, indeed, one cannot altogether eliminate the possibility of a plague attack during the summer in slum areas even of the larger northern American cities. The importance of slums in general as potential loci of bacterial attack is part of the problem of defense against bacterial warfare, as discussed on page 30.

Pneumonic plague and tick-borne rickettsial diseases and relapsing fever are considered in detail in section IV.

The Mosquito-borne Group, and

The Tick-borne Group. All the important agents in both these groups have been considered in section IV, and their epidemiology is discussed individually. Potentially useful agents of warfare are believed to exist in both groups.

Diseases Transmitted by Other Vectors. Except for tularemia, which is transmissible by a wide range of vectors and is discussed in section IV, and bacillar' dysentery, which may be transmitted mechanically by flies, no agents in this group are considered suitable for bacterial warfare. The following have been dismissed from consideration: *trypanosomiases* and *leishmaniases,* because d difficulties in handling the causative agents and accumulating them in sufficient amounts; *papataci* or sandfly fever, because of the exacting requirements of the vector, which lives only 10 to 14 days, requires two feedings to infect, but may feed only once; and the *tsutsugamushi* group of rickettsial diseases, because of inadequate knowledge thus far available of their epidemiology.

THE MEANS OF OFFENSE IN BACTERIAL WARFARE

The writers can presume to discuss this subject only as bacteriologists, not as military experts. They can offer certain suggestions based on their knowledge of the agents of bacterial warfare and of the manner in which these agents may incite and spread disease. The practical problem, however, is one of military engineering, and both its broad outlines and its details remain to be checked and amplified by experts.

The following discussion deals with two general aspects of this question: the military means themselves; and the military purposes which these means may be expected to accomplish.

The Military Means

Under this head are considered means of (a) production, (b) assembly, and (c) dissemination, of infective agents.

Production. Details of methods for the cultivation or otherwise for the accumulation of individual agents are given or referred to for each agent considered, under the head of *availability,* in section IV. Most of these are standard laboratory procedures which are usually undertaken on a small scale; however large scale applications are generally feasible and have been referred to in several instances. For other than experimental military purposes, for which normal small-scale procedures may be adequate, it would probably be necessary to build or convert plants comparable with commercial vaccine laboratories. The more highly infective agents such as the bacilli of plague or tularemia or the viruses *of* yellow fever or psittacosis may require that an entire isolated building of suitable size be devoted to the preparation of a single agent. The layout, equipment and personnel of such plants must be determined to meet the particular requirements of each agent, and cannot be discussed advantageously in generalizations, except that more than the usual precautions will be required.

A general principle of some potential importance concerns the selection, during the course of repeated subcultures and animal passages, of highly virulent or drug-resistant variants, or both. The possibility that strains with unusual properties might be developed by such means should be one of the problems studied by a military experimental unit.

A ssembly. Types of containers for infective agents and the manner of assembling or packing them depend on the nature and physical state of the agent and on the use to which it is to be put. Culture preparations of bacteria or viruses intended for either the water-borne or the indirect contact routes might be dispensed, either in liquid suspension or in dry form as may be indicated, in large thin-walled glass ampules. These might then be packed in sawdust in outer containers for safe handling, arranged so that the bottom can be removed before discharging the ampule over the target. To insure the breaking of such an ampule on contact with water, a gas-generating element like those used in fire extinguishers might be included in the ampule, which would then be weighted at the upper end and maintained upright until discharged. An alternative containe for water-borne agents in dry form, such as botulinus toxin, might be made of porous paper impregnated with a water soluble gum or pectin, perhaps protected for safety in handling by a metal frame heavy enough to sink the container.

The possibility of using projectile contaminants has been mentioned on page 19. If this method of assembly is found feasible the agent should probably be incorporated in the projectile rather than merely applied to its surface, in, order to provide a sufficient quantity of the agent and for the safety of those handling the projectile before discharging or firing it.

For air-borne agents the problem of assembling them in suitable containers is part of the larger problem of means for their dissemination, which is considered 'below.

Containers for infected vectors must be so constructed as to permit survival of the vector inside for the required periods, and to allow safe landing from aircraft and insure liberation of the vectors on the ground, along with the usual requirement for safety in handling up to the point of discharge. The method of discharging infected fleas attributed to the Japanese (Editorial, 1942) suggests a crude device whereby these insects were liberated at the plane itself. Adequate safety as well as greater effectiveness would seem to require somewhat more elaborate measures. Pasteboard or other light containers, either small or with large surfaces to slow their descent, suitably perforated and screened if necessary, perhaps with one weighted and fragile point to assure breakage on landing, might serve the purpose.

Dissemination. Aircraft appear to be the most useful means for dissemination of all agents, whether the agent itself is capable of spreading by the air-borne route or not.

For the dissemination of agents other than the air-borne group from aircraft no requirement suggests itself other than the simple discharge of the appropriate container over the target, with or without automatic devices to increase aiming precision as circumstances may indictae. The dissemination of air-borne agents, on the other hand, is a special problem, but one on which only the most tentative suggestions can be offered without experimentation.

One of the less toxic smoke screen agents like titanium tetrachloride 'might possibly be used as a vehicle, and if such medium is feasible it might serve the dual purpose of disguising the nature of the attack and preventing too rapid dissipation of the agent in the open air. Another possible vehicle is glycerin, which has the advantage of being an excellent preserving medium for many bacteria and viruses. It may also prove practicable to spray desiccated bacteria or virus preparations without any medium other than the nutrients in which they were dried. Two ounces of crude oil are said to yield 1000 cu. ft. of standard naval smoke. If means can be found to distribute dried infective agents so that the individual particle size approaches the order of magnitude of such smoke, a cloud might be produced having similar dispersal properties but of much lower and perhaps negligible visibility. A fine dust of lyophilized material might even scatter sufficiently if merely dropped in a glass vessel.

Dissemination of infective agents via contaminated projectiles, if feasible *at* all, will be determined by the nature of the projectiles, whether they be aircraft bombs, artillery shells, or even small bombs of the hand-grenade type. Whether the last might be used at all is a question related to that of the dissemination of infective agents by individual carriers or saboteurs. While such methods are undoubtedly practicable in appropriate circumstances, they are likely to be very limited in scale and call for no detailed comment.

The Military Purposes

For close fighting with rapid movement. Like chemical warfare, bacterial warfare will probably not be found suitable for engagements in which opposing troops are in close contact or where there are rapid changes of position. A possible exception may be found in the use of agents such as the viruses of measles or yellov fever, or perhaps psittacosis, where the attacking troops might be picked men who had recovered from measles or had been actively immunized against the other diseases. Assuming that air-borne dissemination is possible for all three agents, it may be found feasible to provide adequate protection to the attacking troop' by such means, perhaps supplemented by light face masks with raw cotton *or* other simple filtering pads.

For the reduction of isolated strongholds. For island naval or air bases, or other areas where the military objective is to make them useless to the opposing force, but which need not be captured or occupied by the attacking force, bacterial warfare provides the most notable advantages and is most free from tactical dibadvantages. Any agent suited to the climatic and other circumstances of the terrain could be used, including agents of the greatest potential retroactivity' such as those of plague, influenza or malaria.

In connection with the siege of cities or other static warfare. Either side might employ bacterial warfare effectively under these conditions. Reduction of ° city fortress by a besieging army, where the objective is to bypass rather than to capture the city, would be a problem similar to that mentioned in the preceding paragraph, except that precautions would have to be taken to prevent the spread of a highly epidemic disease beyond the limits of the city. The force within the city might use similar means, with similar precautions, to break a siege against it. Again, under favorable climatic conditions, the agents of measles, psittacosis or yellow fever might be used, as well as any of the less highly retroactive agents, such as those of botulism, brucellosis, tularemia, leptospirosis, and the tick-borne diseases. Mosquito-borne dengue fever virus might also be used advantageously in the temperate zone in late summer or fall, when it may be predicted that weather conditions will favor epidemicity only for a short period.

For the disorganization of industrial areas well within enemy territory. Objectives of this kind are almost as well suited to bacterial attack as are isolated strongholds. The particular circumstances might make it inadvisable to use highly retroactive agents such as plague; but other air-borne agents may find their most favorable applications here because of the concentration of persons indoors and the usual location of such areas in temperate or cold regions. Botulinus toxin might be used in reservoirs feeding these areas.

For army camps and training centers. Such situations are similar to the preceding, except that the density of the population is likely to be lower, the indoor environment relatively less prominent, and the climatic conditions more varied. Air-borne agents of high infectivity used in these situations would be directed particularly against barracks during the night. If swimming pools or ponds were present, leptospirosis and botulism would be indicated. Under appropriate conditions dengue virus might be one of the most suitable agents for these locations.

In connection with strategic retreats or the application of the "scorched earth" policy. For such purposes a persistent agent with little tendency to spread seems to be required, and one which would be least likely to be retroactive in the event that the enemy, after passing through the infected region, subsequently made contact with the opposing forces. The agents of anthrax, brucellosis and tularemia, the tick-borne infections, and perhaps the water contaminants, may all find applications in appropriate circumstances in this category.

For application against useful animals, and against food plants and industrial crops. Some of the most important applications of bacterial warfare may fall in this category, which upon further investigation will probably be divisible into several classes. In addition to the agents listed as specific animal or plant pathogens in section IV, several agents pathogenic for man may also be used against animals, especially those of brucellosis, anthrax and glanders.

'TIIE MEANS OF PROTECTION AND DEFENSE AGAINST BACTERIAL WARFARE

What has been said about the offensive means and purposes of bacterial warfare suggests many of the necessary precautions for defense and protection. Here again only the broad outlines can be indicated, subject to review and amplification by specialists particularly in thelelds of military and public health engineering and sanitation.

The term "protection" is used here to indicate the means used by a military force employing bacterial warfare to safeguard its own troops against the agent; "defense" to designate measures taken against agents used by the enemy.

Protection against retroactivity. Several means of protection have already been indicated. They include necessary safeguards in the preparation, assembly and dissemination of agents; the skillful selection of agents to suit the military purpose; the selection or immunization of attacking troops; the use of suitable face masks or of mosquito-proof or other vector-proof clothing where indicated, Additional measures overlap those considered below, and would be applied by an attacking force on entering an area previously subjected to bacterial attack: avoidance of contact with cases, presumed carriers, water or other materials likely to be contaminated according to the agent and the manner of its dissemination; and suitable measures of sanitation, such as disinfection and vector control.

Defense against attack. This is undoubtedly the largest and most difficult problem in bacterial warfare, and one upon which all the material in this report bears directly or indirectly. It has additional features that have not otherwise been dealt with. The problems of defense fall into three groups, namely, anticipation and warning, detection and identification of agents, and means of control. The first two subdivisions are conveniently considered together.

Anticipation and Warning; Detection and Identification

In well organized communities and in modern military organizations several routine sanitary measures may serve, with or without amplification, to anticipate and to identify the nature of a bacterial attack and thus to put into motion the machinery for control. Water sanitation is particularly well developed in this country, and for this reason, as noted previously, water-borne agents have been relegated to a place of subordinate importance in bacterial warfare. Existing means for warning and detection of air raids may also be adequate; perhaps special precautions are needed to meet the fact that an enemy plane loaded with containers of infective agents may be just or nearly as dangerous if shot down over friendly territory as if it were allowed to pass unharmed—unless it were totally burned. Police surveillance for the detection of sabotage would also apply directly. Likewise the available health service facilities, both public and private, could be used for the detection and identification of the most common diseases.

It is evident that these existing measures are inadequate. New procedures are needed, both for anticipation of attacks and detection of agents, and for detection and identification of their effects.

The fact that one or more planes has flown over an area, particularly at low altitude, without dropping bombs or for any other evident purpose, should in itself arouse the suspicion of a bacterial attack. The warning should be made general that anything apparently dropped by such a plane, however insignificant it may look, should be treated with the respect accorded a floating mine washed up on a bathing beach. An immediate method of treatment of such objects, applicable by the untrained, such as covering them completely with earth or sand, should be devised and ordered. Provision should then be made for collection of the objects by decontamination squads trained to suspect their possible character and to use the necessary precautions in handling and transporting them to laboratories for identification.

More specific new measures include the following:

Water pollution tests. It has been indicated on page 16 that conventional tests for fecal pollution of water are inadequate against bacterial attacks because they depend on the presence of the colon bacillus, which will certainly not be included in any material used for deliberate pollution. The need for additional tests will not be entirely obviated even if it can be shown that existing methods of filtration and chlorination are capable of destroying all the potential water-borne agents; since they may conceivably be used following a bombing attack beyond the filtration and chlorination points, or the latter may be put out of service. Mackenzie (170) mentions this question as part of the problem of the protection of London's water supply against bombing, chemical and bacterial attack. Additional tests are plainly needed. It is recommended that such tests be principally of the animal pathogenicity type, using guinea pigs and mice as animals of the broadest susceptibility, inoculated by several routes including the intracerebral. Water for such tests should be used without treatment of any kind, and after attempted concentration of the agent by evacuation at low temperature, centrifugation, or other suitable means. Positive results should have presumptive identifying value on the basis of symptoms, pathology, and direct miscoscopic examination of animal material. Such results should be followed up with protection tests, cultivation or other measures indicated by the initial findings. The peculiar possibilities dependent upon artificial attack should be kept clearly in mind by the laboratory staff: unusual diseases, those not known to be water-borne, and mixtures of pathogens in a single sample.

Air-pollution tests. Tests of air and dust for their bacterial or virus content are not in general use, and have not been standardized, although experimentation in this field has been active in recent years and has furnished both instruments and procedures that could probably be applied for this purpose. Most if not all devices for sampling air bacteria, of which the Wells air centrifuge is the one best known, do not directly indicate the presence of agents difficult to cultivate. However, these devices could probably be adapted for such agents, including viruses, which might be collected in liquid suspension and then treated by methods suggested in the preceding paragraph.

Tests for other agents. Agents of the indirect-contact and vector groups collected in sweepings or in their containers should offer no particular difficulties in identification. Preliminary identification of the vector would suggest suitable tests for identification of the agent.

Detection of unusual diseases. Many peculiar and unusual problems of diagnosis may arise under conditions of bacterial warfare, which require more consideration than the scope of this report warrants. The general principles seem to be (a) the need for well informed suspicion of unusual diseases, of more common diseases transmitted by unusual routes, and hence perhaps atypical in symptomatology, and of artificially mixed infections whose symptomatology may consequently be unusual even though the component diseases may not be; (b) the need for information on these possibilities and on means for their detection, to be widely disseminated among both military and civilian physicians, especially those of the latter located in importnt industrial areas; and (c) the need for

development of such additional laboratory and other diagnostic tests as naay required to facilitate diagnosis, and of means for application of such tests.

Parallel tests and methods for animal and plant disease agents. Methods for surveillance of livestock and crops, and for identification of infective ag, used against either, might follow the general outlines suggested above. Lai farms or ranches (where attack is most likely) may find it difficult to secure suitable technical assistance for these purposes.

Control of the E,ffects of Bacterial Warfare

Measures that seem indicated for purposes of control of outbreaks or epidemics of disease resulting from bacterial attack may be considered under three heading ,' those to be applied immediately in the emergency arising out of an effective attack; those of a permanent or semi-permanent protective character; and tho, whose objective is of longer range, aimed to make bacterial attacks less effective.

Emergency or immediate measures. In the sense of preceding paragraph ', existing public and private health service facilities may require amplificatioil- or mobilization in the event of an attack. One means toward this end might the organization, in every large military establishment and in every industr, center, of medical bacterial warfare units analogous to chemical warfare units, with provision to insure maximal mobility. The unit, cooperating with local health, police and civilian defense agencies, should have power to enforce isolation and quarantine either of individuals or of entire districts, and if necessary t - evacuate unaffected groups. Anti-bacterial equipment, such as masks arid screens, and material for mass immunization and other prophylactic or therapeutic measures, should be made available. The general dissemination of information on individual sanitary and other precautions following the first presumptive identification of the agent in use might also be the responsibility of suck units. Training of civilian defense agencies such as air and fire wardens for use as bacterial decontamination and identification squads would be valuable.

Permanent or semi-permanent measures. Provision of permanent or semi - permanent facilities for prevention, particularly of air-borne infection, deserves serious consideration, as it does, indeed, in relation to the general problem of the inadequately controlled respiratory diseases. The use of antibacterial aerosol sprays or of ultraviolet lamps in the most vital susceptible areas, such as barrack' and factories, or of other measures to prevent or limit the passage of infective agents through the air, seems to be indicated, from both viewpoints. There mud also be need for precautions, in addition to those now used routinely, for the disinfection or sterilization of water and food.

Long-range measures. Areas of congestion and of poor social hygiene in tile broader sense of that term are breeding grounds of natural epidemic diseases. From what we now know of the epidemiology of such diseases, particularly is the light of the newer concept of air-borne infection, it may well be doubted whether they will ever be brought adequately under control except by means ef broad social public health measures rather than individual public health measure s. This view seems to apply with particular force to the great respiratory epidemic diseases, against which sanitary controls are less easily applied than they are against the water-borne diseases, and in which immunization has thus far been almost universally unsatisfactory.

It would seem foolhardy in the extreme to suggest that the possible consequences of a bacterial attack in such areas of congestion can be dismissed lightly. In preceding paragraphs, the needs of the military and industrial forces have been considered as immediate problems. The needs of the population at large are hardly less important, but they are admittedly much more difficult to deal with. The emergency measures that have been indicated will certainly not meet them adequately. It is obvious that consideration must be given to this problem. Its extent and importance are far beyond the limited scope of this report.

It may be that the more widespread use of air conditioning or filtration, or of sterilization of air in civilian congestion areas, might be of significant value. On the other hand it is possible that nothing will solve the problem short of widespread slum clearance on a much larger scale than has been contemplated even in recent years.

A more specific question in this field hinges on the discussion of malaria (page 74) as a possible consequence of bacterial warfare in an area of military importance which is now free from the disease but affords conditions suitable for its spread. Malaria control measures seem indicated in such areas in advance on the broadest possible scale.

IV. THE POTENTIAL AGENTS OF BACTERIAL WARFARE

CRITERIA FOR THE SELECTION AND APPLICATION OF AGENTS

Infective agents were selected for consideration of their potential value in bacterial warfare, on the basis of the following criteria. They serve as section headings for the subsequent discussions of individual agents.

1. *Infectivity.* Susceptibility, resistance or immunity ;attack-rates, if available; evidence from accidental laboratory infections.
2. *Casualty effectiveness.* General degree and character of immobilization produced by the agent; incubation period, severity and duration of course and convalescence; case mortality.
3. *Availability.* Cultivability on ordinary or enriched media, or in tissue or egg culture; maintenance in vectors, experimental animals, or by other means. Mass production methods if available; stability of virulence.
4. *Resistance.* Methods for maintenance of virulence for long periods, if available; means of disinfection.
5. *Means of transmission.* Known natural routes of transmission, common and alternate; evidence for possible additional means of transmission, if available.
6. *Epidemicity.* Capacity for spread from man to man or animal to animal; possibilities under artificial conditions.
7. *Specific immunization.* Availability of means for immunization; effectiveness.

8. Therapy. Specific therapy and chemotherapy; availability; effective

9. Detection. Means for identification of the agent and for bacteriol diagnosis of the disease; ease or difficulty of detection.

10. Retroactivity. Likelihood and probable degree of danger in use to an et a ing force; means of protection or control.

LIST OF DISEASES WHOSE AGENTS HAVE BEEN SELECTED FOR CONSIDERATIO N

Page References Indicate Discussion of the Disease in the Text

Anthrax, 42
Botulism, 33
Brucellosis, 64
Common cold, 48
Dengue fever, 71
Dysentery, bacillary, 41
Equine encephalomyelitis, 81
Foot-and-mouth disease, 81
Fowl plague, 82
Glanders, 55
Hog cholera, 82
Infectious laryngo-tracheitis of fowls, 82
Influenza (virus with *H. influenzae),* 48
Leptospirosis, 36
Louping ill, 83
Malaria, 74
Melioidosis, 57
Meningococcus meningitis, 52
Mumps, 50
Newcastle disease of fowls, 83
Pasteurellosis (hemorrhagic septicemia), 83
Plague, pneumonic, 45
Plant diseases, 84
  Bacterial canker of tomato, 85
  Bean blight, 86
  Black rot of crucifers, 85
  Black rot of potato, 86
  Cureurbit wilt, 85
  Brown rot of solinaceae, 86
  Fungous diseases, 86
  Insect diseases, 87
  Virus diseases, 86
Pleuropneumonia, bovine, 80
Psittacosis, 53
Relapsing fever, tick-borne, 75
Rickettsial disease, tick-borne, 78
Rift Valley fever, 69
Rinderpest, 83
Tularemia, 61
Yellow fever, 69

LIST OF DISEASES WHOSE AGENTS HAVE BEEN REJECTED, WITH REASONS

Actinomycosis, endogenous
Cholera, sanitary precautions, immunization
Diptheria, low attack rate in adults
Dysentery, amebic, availability poor
Endocarditis, subacute bacterial, endogenous
Friedlander pneumonia, low infectivity (except in combinations)
Fungous diseases of man and animals, casualty effectiveness low
Gas gangrene, ubiquity (except as projectile contaminant?)
German measles, unavailable
Gonococcal infections, non-venereal infectivity low
Leishmaniases, unavailable
Leprosy, long incubation period, chronicity
Lymphocytic ehoriomeningitis, low infectivity (?), insufficient data
Papataci fever, exacting requirements of vector
Pertussis, low infectivity for adults
Plague, bubonic, predisposing social factors, complex epidemiology
Plant virus diseases, several years required to decrease yield
Pneumococcus pneumonia, low infectivity (except in combinations)
Poliomyelitis, unavailable, low infectivity
Rabies, low attack-rate, long incubation period, difficulty of transmission
Rat-bite fever, difficulty of transmission
Relapsing fever, louse-borne, availability poor, predisposing social conditions
Salmonella infections, low infectivity (except animals, or combinations)
Smallpox, vaccination
Staphylococcus infections, low casualty effectiveness (except combinations)
Streptococcus infections, low infectivity (except combinations)
Tetanus, immunization
Trench fever, etiology unknown
Trypanosomiases, unavailable
Tsutsugamushi disease, epidemiology inadequately known
Tuberculosis, chronicity, low casualty effectiveness
Typhoid fever, sanitation, immunization
Typhus fever, availability poor, predisposing social factors
Varicella, unavailable
Venereal diseases, dissemination impracticable
Vincent's angina, endogenous
Wound infections, anaerobic, ubiquity of agents (projectile contaminants?)

AGENTS SELECTED FOR DETAILED CONSIDERATION

Agents of Predominantly Human Diseases.

Water-borne Diseases.

Botulinus Toxin

Clostridium botulinum and its toxins might be employed as agents of warfare by two general means: first, the deliberate contamination of foods in the process of canning or preservation, with the organisms or their spores; and secondly, the dissemination of the toxins themselves. The former method could be attempted only by saboteurs. In large canneries under modern conditions of mechanical processing, it is doubtful whether it could be applied at all; certainly a well organized group would be needed. Furthermore, if it were successful at all, such an approach would be small in scale and could hardly be repeated. On the other hand, preformed toxin might be disseminated from the air for pollution of reservoirs or other drinking water supplies. It is this application which seems to deserve close consideration. This use of toxin as a preformed poison would be as much a part of chemical welfare as of bacterial warfare. Experts on the former subject and sanitary engineers may have data on botulinus toxin which are not available to the writers. As far as our data go, botulinus toxin appears to be eminently suitable for this purpose.

Infectivity (Human susceptibility). Botulinus toxin appears to be theoN st potent of all gastro-intestinal poisons, by a wide margin. The actual mink,' lethal dose for man by the oral route is not known, but can be estimated rouad y from experimental data. It may be noted that Dickson (59) has reported that severe illness or death has resulted from merely tasting contaminated food, withq ut swallowing an appreciable amount, suggesting that human susceptibility the oral route is very high. The most potent toxin preparation of Sorar b ,, (254), who reported methods for mass production of toxin to be noted later, ilad an m.l.d. for the mouse of 2 X 10^{-}' gram per kilogram by the subcutaneous rout e Assuming equal susceptiblity, the human m.l.d of this product may be estimat ed as of the order of 2 X 10^{-5} gram. Since Dack and Wood (51) found that th, lethal dose for Macacus rhesus monkeys *by mouth* was less that the weight4o,.. weight equivalent m.l.d. for the mouse *intraperitoneally,* the human oral m.1 ,1l, may not be far from the value given. From data tabulated by one of the autl1Q,, 5 in Gay (101), the equivalent dosage of potassium cyanide appears to be at le ast ten thousand times as great.

Data from many outbreaks of botulism in man indicate that, with rare ceptions, all who partake of food containing the toxin become ill, suggesting attack-rate close to 100 per cent.

Casualty effectiveness. The incubation period of botulism is much longer th all that of non-biological poisonings, but short in comparison with most infectiok,, from 9 or 10 hours (156) to 3 days or more. The earliest symptoms are usuqh, indisposition, fatigue, headache and dizziness, sometimes with gastric distr,' Severe neuroparalytic effects develop, with early disturbances of vision 4 1n1 secretion, and later progressive musclar weakness. There is usually little or pain other than the initial headache and variable gastric upset. Death occurs in from 24 hours to 10 days, or recovery requires 2 to 4 months, usually progressing to completion without sequelae. Case mortality has varied from 16 per cent in Germany (14) to 66 per cent or more in the United States (177) and Russia (306). In more recent outbreaks in the United States described by Hall (115), the mortality was 82 per cent.

Availability. Preparation of botulinus toxin in small amounts by cultivation of *Cl. botulinum* in suitable fluid media presents no especial difficulties. Thee, organism is a strict anaerobe and requires enriched media. Dubovsky and Meyer (63) and Dack, Starin and Werner (50) give technical details; according to the latter workers, CO, should be included in the gaseous environment of the culture. Growth and toxin production are most rapid at 37 C.; but acording to Tanner and Oglesby (273), toxin appeared slowly even at 15 C. though not at 10 C. Soratner (254) has devised a procedure which is "recommended for the preparation of relatively large amounts of highly potent botulinus toxin. It makes use of the most simple equipment and reagents", and is adapted to carboy lots. By further calculation from the potency data (254), about 350 pounds of a preparation of such purified toxin would contaminate a ten million gallon reservoir so that, if, it were evenly dispersed, every 5 c.c. unit would contain an estimated human minimal lethal dose. As Goudey (109) remarks in a recent paper on wartime protection of water supplies, a single large airplane or a fleet of small planes could place ten tons of (other) poisons in a reservoir in a single attack. While 350 pounds of botulinus toxin may seem an impossibly large amount to one accustomed to small-scale research laboratory yields, it seems not inconceivable that unit amounts of this magnitude would be well within the capacity of large serum laboratories devoted to this express purpose.

It may be noted here that there are at least 5 immunologically distinct botulinus toxins, known as types A to E. Types C and D are not known to be toxic for man, and type E has been described only in recent years (124, 125, 154) and is not as well understood as the others. Types A and B have similar properties (with one notable exception; see detection), and either or both could probably be used for war purposes.

Resistance. That *Cl. botulinum* forms spores which have extraordinary powers of resistance (101) may be noted in passing. Botulinus toxin is peculiar among analogus biological agents in that it resists gastric acidity and both peptic an tryptic digestion, facts which explain its capacity to act by the gastro-intestinal route. It is also fairly resistant to heat, requiring 10 minutes at 73 C. or 6 minutes at 80 C. for inactivation. Prolonged boiling may be required to destroy it in highly contaminated food or where heat penetration is slow. In drinking water, however, simple boiling would probably be sufficient to inactivate it. The toxin does not deteriorate rapidly in air at room temperature, several months being required to induce detectable loss of potency. It is more stable when stored anaerobically, and can be preserved for five to eight months or more on ice in the dark. It is resistant to freezing and to alternate freezing and thawing (101). We have no data on its capacity to withstand conventional water purification and filtration methods. If such data are not available, experiments to obtain them would seem very desirable.

Means of transmission. In nature botulism results from the ingestion of food, especially canned and preserved vegetables and meat products, previously contaminated with *Cl. botulinum,* and in which the toxin has been preformed. We know of no instance of transmission through drinking water in nature, but there is no reason to doubt that this method could be applied artificially. The possibility of air-borne transmission of dried pulverized toxin may also be considered feasible in view of the minute dose required to induce the disease.

Epidemicity. Botulism is a non-infective intoxication; the organism itself appears to be entirely non-pathogenic.

Specific immunization. Botulinus toxoids have been prepared by several workers by the prolonged action of dilute formalin (162, 141, 288). Velicanov (288) vaccinated 40 human subjects with toxoid, using 5 injections (2 doses of 0.5 c.c. and 3 of 1 c.c.) at intervals of 10 to 12 days. Twelve days after the last injection antitoxin was demonstrated in the serum by protection tests with guinea pigs. Three injections of toxoid were found insufficient. Nine subjects vaccinated with 5 injections were revaccinated after a year with a single injection, and showed a considerable rise in antitoxin titre. Melnik and Starobinetz (176) have prepared and recommended an alum-precipitated botulinus toxoid.

Therapy. Serum therapy is used, but no controlled data on its value are avail-

able. The serum should be bivalent: active against both types A. and B toxin. Weinberg and Kreguer (294) have reported production of high-titred bivalent sera in horses by the lanolin-emulsion method of Ramon.

Detection. The problem of detecting botulism for protection against attack is less a matter of diagnosis in the individual case then of identification of the toxin in reservoirs or other environmental media. The addition of a routine test of for this purpose to standard waterworks practice in wartime is suggested. In vitro tests such as the complement fixation reaction (264) are probably to be desirable than animal tests. For the latter the mouse seems the most suitable animal, although guinea pigs are about equally susceptible. A mouse test could might be employed to detect the toxin and identify its type. Preliminary vacuum desiccation in the cold might be desirable to concentrate the toxin. The development of a test adapted to this specific purpose by direct experiment is indicated.

Another means to detect botulinus toxin in reservoir water might consist in the maintenance of a small colony of white mice at the site. Chickens might also be used for this purpose; they develop symptoms 3 or 4 hours after ingesting toxin, and generally die in 24 to 36 hours. Chickens, however, are susceptible to type A but not to type B toxin (110).

Diagnosis of botulism in man depends on clinical signs, commonly aided by history and demonstration of toxin in food. Blumberger and Gross (18), however, suggest intraperitoneal inoculation of 2 to 5 c.c. of the patient's serum into guinea pigs. If circulating toxin is present the guinea pig develops characteristic salivation and paralysis 24 to 48 hours later.

Retroactivity. Since botulinus toxin is not an infective agent, its retroactivity would be a function of persistence only. It is probably the least retroactive of all agents of bacterial warfare.

Leptospira Icterohemorrhagiae

Among the several leptospira varieties pathogenic for man distinguished in the literature, which differ serologically and in their relative virulence, only the most active, the spirochete of Weil's disease, need be considered here in detail. It is suggested that the organism of choice would be isolated from a human case of the disease, preferably one showing icterus, and that it would be uniformly pathogenic for the guinea pig.

Infectivity. The attack rate of leptospira infection in man is difficult to define from data on natural outbreaks because of the peculiar epidemiology of the disease. Except for laboratory infections the disease seems always to be spread through water or food which has been contaminated by animals, particularly wild rats, or through direct contact with such animals, notably by rat bite. These circumstances underlie the predominantly occupational character of outbreaks. Under such circumstances it is rarely if ever possible adequately to determine the number of persons exposed. Alston and Brown (1) estimated that the attack rate is low, from the fact that only 18 recorded cases occurred among 1000 sewer workers in London during a two and a half year period. All the workers were assumed to be exposed because of the known prevalence of infected rats and of contaminated water ; but this assumption may have been unwarranted. Jorge (144) described a water-borne outbreak in Lisbon in 1931, in which 128 or more cases were associated with a fountain fed by an open conduit known to have been contaminated by rats from a neighboring sewer. Again, however, the number of persons exposed, and the number who may have developed subclinical or otherwise undiagnosed infection, are unknown.

The fact that laboratory infections seem to have been frequent (267, 229) is suggestive of high infectivity. A more striking suggestion to the same effect is implied by the data of van Thiel (286), given more fully under resistance: all of 5 human subjects inoculated subcutaneously with a supposedly attenuated living vaccine became infected. On the basis of this experience van Thiel considered man more susceptible than the guinea pig, contrary to common opinion. The view seems to be gaining ground that leptospira infection is much more common than published American statistics would suggest, and that it is frequently missed or wrongly diagnosed (159). In view of these facts the possibility of its use as a military agent should not be overlooked, and it has been selected for detailed consideration accordingly.

Hull (136) states that the disease is rare in children, despite opportunities for exposure. Otherwise its predilection for certain occupations, and its tendency to occur in summer and fall rather than during other times, all appear to be functions of its natural epidemiology and are not particularly significant here. Weil's disease is known to occur throughout the world in all zones except the frigid.

Casualty effectiveness. Weil's disease varies considerably in severity, but disease associated with typical *L. icterohemorrhagiae* seems generally to be a prolonged and prostrating illness. In its more severe form as described by Japanese workers (140) it includes fever as high as 105 F., icterus appearing on the 7th or 8th day of illness, with death during the second or third week in as many as 32 per cent of instances, or convalescence proceeding over several additional weeks. According to Schaffner (227) about 60 per cent of patients do not show jaundice, and such cases recover. The onset is sudden, with severe muscular pains, often with meningeal symptoms. The incubation period is generally about 1 week, rarely as long as 2 weeks. Mortality has varied in different outbreaks from 4 per cent or less in Europe during the first World War to as much as 50 per cent in Japanese outbreaks.

According to Uhlenhuth and Fromme (283) there were 70,000 cases of Weil's disease ,among troops in the American Civil War, estimated as 2 to 2.5 per cent of the total army strength; and the disease was also common among troops of both sides in the trenches on the western front in the first World War (173).

Availability. Cultivation of pathogenic leptospiras is now practiced routinely and with ease in many laboratories. The organisms are aerobic; they grow near the surface of appropriate liquid or semisolid media and appear in large numbers in a few days at moderately warm room temperature (22-30 C.) rather than at 37°. They apparently do not easily lose virulence in culture for either guinea

pigs or man. Media which have been used successfully include those described in the following references (198, 228, 284, 289). Noguchi (199) devised a method for mass cultivation of leptospiras, utilizing a layer of semi-solid medium 1-2 era deep in a large flask, and reported that within two or three weeks leptospiras were present to a concentration of 16 billion per c.c.

Leptospiras have also been grown on the chorio-allantoic membrane of the chick embryo without loss of guinea pig virulence (189, 57, 35).

True *L. icterohemorrhagiae* (as distinguished from L. *canicola)* appears to 13(uniformly pathogenic for the guinea pig, generally killing the animal within S or 9 days with pronounced jaundice of skin and conjunctiva, and with spirocheto readily demonstrable in the liver, kidney, adrenals, and probably also in the testicles and brain (146). Deer mice (204) and very young white mice (157) arc also easily infected, but other animals appear to be less suitable. Several worker (266,198,146) have reported that virulence for guinea pigs could be enhanced 1,)•' passage; but it is not known whether such enhancement affects virulence for mai)• It has been suggested (146) that *L. autumnalis* and L. *hebdomadis* seemed to be transformed by guinea pig passage so as to become serologically indistinguishabk from *L. icterohemorrhagiae,* although other antigenic variants retained their specificity.

Resistance. Leptospiras are easily destroyed by heat and disinfectants, and are particularly sensitive to moderate salt concentrations and to acidity. Thai are thus not found in sea water or in brackish waters even though alkaline (1) and do not survive at pH levels below 6.6 to 6.8. They are easily destroyed bi gastric juice, and also by bile (276). Turner and Fleming (282) were unable tC' maintain virulent leptospiras by the solid COT-ethyl alcohol method which Turner (280) used successfully for other spirochetes and viruses. Topley and Wilson (276), on the other hand, state that leptospiras can withstand freezing.

Leptospiras have nevertheless been found to remain virulent for 7 days iu defibrinated blood exposed to daylight at room temperature (283), and after 20 days in infected guinea pig liver stored in the ice chest (26). Van Thiel (286) states that L. *icterohemorrhagiae* survived with intact virulence for at least V days in water during warm weather. They are said to survive in moist soil for 3 months (267).

Maintenance of virulence for man in culture is attested to strikingly by the experience of van Thiel (286). This worker attempted to use as a living at- tenuated vaccine a strain of *L. icterohemorrhagiae* which had been maintained culture for eight years without animal passage, and was practically avirulent f guinea pigs. He inoculated himself and four other persons. subeutanemrly. All five underwent atypical attacks of infection, nearly symptomless in two mild in two others, and severe enough in the fifth to put the subject to bed.

The capacity of leptospiras to grow at room temperatures should be considered in relation to bacterial warfare: they could be maintained and transferred in the field in warm weather without special equipment.

Means of transmission. Leptospira icterohemorrhagiae is transmitted in nature' chiefly through water contaminated by rat urine, and infection of man occurs by ingestion or by bathing in or falling into contaminated water, or otherwise by contact of such water with skin abrasions or the mucous membranes of mouth, respiratory tract or eye. Infection has also followed rat bite. All these routes, as well as subcutaneous or intraperitoneal inoculation, can be used successfully in the guinea pig. It has been noted (1) that unpremediated immersion in contaminated water is likely to be more dangerous than bathing because of struggling and the consequent entrance of water into the respiratory tract, and that the "crawl" stroke in swimming may be more dangerous than other methods for similar reasons.

Strong (267) remarks that water may be infectious and yet appear clear, since leptospiras are not necessarily associated with organic decomposition or massive pollution. This would be particularly true for artifically contaminated water.

There is no evidence that *L. icterohemorrhagiae* can or might be transmitted by any route other than those mentioned. As an instrument of war its use would seem necessarily confined to the contamination of food or more particularly of water, including both drinking water and enclosed fresh water ponds or pools used for bathing or swimming. For one or another of these purposes it might be combined with other agents in the water-borne group, or with the bacilli of tularemia or of undulant fever.

Epidemicity. Although Weil's disease has occurred in outbreaks which have been spoken of as epidemic, it does not appear to be transmitted easily if at all from man to man. The epidemiological character of the disease supports this view. Leptospiras are excreted in the urine of man as in that of infected rats and guinea pigs, but they seem not to be released into the environment in any other way. Even in a severe outbreak with many cases ordinary sanitary precautions should therefore suffice to prevent spread of the disease; and in the event of a successful attack—unless the attack were so successful as to disorganize sanitation—all the cases would probably be restricted to those in- fected from the initial sources. As noted below, however, early recognition of the disease might be essential to insure limitation of the extent of such an outbreak, not only because the causative agent might-persist at the source, if this happened to be a stagnant pond, but also because urinary excretion of leptospiras may continue for long periods. Spirochetes may begin to appear in the urine about the 5th day of illness and continue frequently for 20 days, sometimes for as long as 60 days (140).

Specific immunization. Recovery from Weil's disease is followed by definite and lasting immunity associated with the development and persistence of anti- bodies in the blood. Vaccination with killed cultures has been used with apparent success in Japan (290) and elsewhere. Schaffner (229) recently reported that his laboratory staff had been immunized with 2 intravenous injections a week apart of killed culture, after a laboratory infection by rat bite.

Other protective measures. The known sensitivity of leptospiras to moderate heat and to acidity provide useful leads to means for protection against them or

for rapid control of an outbreak. *L. icterohemorrhagiae is* destroyed by heat at 50-55 C. for 30 minutes (276). Cooking of food and boiling of drink water would thus be an adequate safeguard. No direct data on chlorination have been seen, but this method would seem promising, and after suitable I might be used for disinfection of both latrines and bathing places.

Therapy. Arsphenamines are known to be ineffective in the treatment, leptospira infections. Specific antiserums have been widely used, however, are apparently valuable if given during the first few days of infection, bet jaundice appears. Convalescent human serum, goat antiserum (138, 139) , horse antiserum (173) have been used. A polyvalent horse serum has been l ommended for treatment in severe cases (267). According to Elander and A (70), K. F. Meyer has made available a serum for treatent of dogs.

Detection. As previously noted, rapid diagnosis of leptospiral infection wp be important under conditions of attack to preclude the possibility of spread otherwise to make it possible to bring the outbreak under control. Such ra diagnosis could probably be made only if the disease were suspected and adeq facilities for its detection were at hand, since the clinical symptoms, in frequent absence of jaundice, are varied and not especially revealing. Th, is evidence that Weil's disease frequently goes unrecognized. Larson (lise considers that the spotty distribution of 51 cases in Puerto Rico and the Unit States suggests failure of diagnosis, and remarks that "it is a matter of singiq interest that in any given locality the reporting of cases increases with the discovery of a single case."

Diagnosis is essentially a bacteriological problem. During the first few e1, of illness spirochetes are considered to be present in the circulating blood, but tiw, can rarely be demonstrated there by direct examination. Dark-field examinatio: should nevertheless be done, and 2 or 3 c.c. of blood, defibrinated rather thax- eitrated (35), should be inoculated intraperitoneally into young guinea wg., (194), or smaller quantities into deer mice (204) or very young white mice (lv) After about the 6th day of illness (271) antibodies appear in the blood; th reach high titres 14 or 15 days after onset and remain thereafter for many yl, (138, 139). Numerous tests have been devised for their detection, among whiel] the agglutination-lysis test appears to be most widely employed (184, 172). recently suggested macroscopic agglutination test (262) appears to be less eii sitive than the microscopic test, but is perhaps suitable for acute cases. Larson (158) devised a diagnostic protection test in mice.

Retroactivity. It seems apparent from the foregoing that, whatever dent of military success might attend the use of *L. icterohemorrhagiae* as a war weapon. the military unit employing it could be easily aimed against counter-infection even though its own forces entered the attacked territory during the height 07. the outbreak. Armed with knowledge of the nature of the agent, they could avoid infection merely by avoiding contact with materials known or suspected to be contaminated; and having occupied the territory, they could probably quickly disinfect it and make it safe for their own troops by methods such as the or suggested. Preliminary vaccination seems hardly necessary.

Shigella Species (Dysentery Bacilli)

.Although bacillary dysentery is one of the world's great scourges (276) these ,gents seem very limited in their military possibilities. They might be used to contaminate reservoirs and wells as part of the scorched earth policy of a ietreating force, and small outbreaks might be started by saboteurs through contamination of food, milk or water. Normal sanitary precautions, however, Ncould probably prevent large outbreaks in cities or well organized military units.

Infectivity. Two laboratory infections in man have been recorded (276), infection having occurred by ingestion; and other instances are known. The fact that outbreaks particularly of Shigella infection are very common suggests pigh infectivity.

Casualty effectiveness. The incubation period is short, usually about 48 hours. The disease may be very severe, as in the toxic Shiga type, which is frequently fatal, but may vary in intensity down to a transient form hardly more serious than Salmonella food-poisoning. An outbreak of Newcastle dysentery in a Yew York hospital was considered to be more severe than the Flexner and Sonne types (120). Symptoms may last only a few days, or the disease may run a chronic course, with marked inanition and prostration. Arthritis may occur during convalescence.

Availability. All strains of Shigella are readily cultivable in large quantities.

Resistance. Dysentery bacilli are easily destroyed by heat and disinfectants. The Shiga type remains viable in river or aqueduct water for many hours (64), And has been known to live in soil for from 6 to 15 days (305).

Means of transmission. Dysentery is usually transmitted through food or water, but may also be conveyed by house flies; and carriers are an important source of infection. On recovery, persons may often excrete bacilli in the feces, and some become persistent carriers. Shiga (235) states that 30 per cent of convalescents excrete the organism for a considerable time, and that over 9 per cent of familial contacts were carriers. Precautions against dysentery carriers would be similar to those against typhoid carriers.

Epidemicity. Dysentery has been a severe epidemic disease particularly in armies. The most serious outbreaks are those due to the Shiga bacillus. Shiga (235) states that such epidemics have recently become rare in Japan. Seasonal incidence coincides with the prevalence of flies, from whose intestinal contents bacilli have been isolated (276). Outbreaks are frequent in temperate climates, often associated with public institutions such as mental hospitals and orphanages (305). Man-to-man transmission results largely from defective sanitation and inadequate personal hygiene.

Specific immunization. Toxicity of the Shiga bacillus even in killed suspension has prevented widespread vaccination despite early encouraging results (276). The immunochemical studies of Morgan (187) offer the possibility of isolation of an effective non-toxic antigen. Little is known of the chemical composition of other dysentery organisms.

Therapy. Shiga dysentery antitoxin is said to be effective (235), but large scale trials have not been reported.

Detection. Bacteriological diagnosis depends chiefly on isolation of the active organism from the stool, using differential media, and its identification by biochemical and serological tests. Specific agglutination with the patient's serum against known strains may have late or retrospective diagnostic value (120).

Retroactivity. Measures based on foreknowledge of the contamination of the organism should be adequate to prevent infection of attacking troops.

Poliomyelitis Virus

Poliomyelitis virus has been shown in recent years to be capable of transmission by the water-borne route as well as the air-borne. This agent is probably unsuitable for warfare. Its cultivation is still an unsolved problem, and only monkeys provide the only certain laboratory source of active virus, and multiplication of the agent in amounts sufficient for the purpose is not feasible. Infantile paralysis, moreover, appears to have a very low attack-rate in terms of the symptomatic infection, particularly among adults.

Contact infections.

The Virus of Lymphogranuloma Venereum

At the present time not enough information is available about lymphogranuloma virus to warrant its detailed consideration as an agent (191). Kuhn (191) states that its degree of infectivity is not known, nor is much data available on extragenital transmission. The virus is available in tissue culture however, and the Frei antigen is a satisfactory specific test. Sulfathiazole therapy has been successful.

Air-borne infections.

Bacillus Anthracis

The anthrax bacillus is one of the most thoroughly studied bacteria, properties make it an obvious possibility as an agent in warfare. Only those details which seem most relevant to such use are presented.

B. anthracis is surpassed by few microorganisms in infectivity for animals and by none in host range. Martos (175) found with mice that a single bacillus killed 28 per cent, 2 bacilli 50 per cent, and 20 bacilli killed 100 per cent of animals. Farm animals, especially cattle, sheep, goats and horses, are most susceptible; but no mammal appears to be entirely immune, although some like Algerian sheep, are somewhat resistant, and individual resistance varies. Although anthrax in man tends to be less severe than the disease in animals, there is no reason to believe that man is less susceptible to infection. Infection may occur in farm animals from malignant septicemia in two to three bolt more commonly in 1 to 5 days. The incubation period appears to range from a few hours to several days, depending on size of dose and route of administration (276). Excluding very mild outbreaks the death-rate in animals seems to vary from 75 to 100 per cent (276). Pulmonary anthrax in man is almost invariably fatal, but the more common cutaneous type has a case fatality of 5 to 15 per cent. In the United States, between 1920 and 1938, there were 1749 cases with 391 deaths, a case-fatality rate of 24 per cent (45),. Experimentally, infection through the skin or mucous membranes appears to require concomitant injury to the surface, even in the respiratory tract (225). Although a history of a cut or abrasion is not always obtainable in human cutaneous anthrax (74), it is generally considered that a break in the skin is required for infection. Human pulmonary anthrax—"wool-sorter's disease"—is associated with large amounts of infected dust, and a mechanical irritation factor in the infection may be assumed. Biting insects are believed by some to be capable of transmitting anthrax (136). Instances of transmission from man to man are known (136), but direct transmission from ease to case is certainly unusual even with animals. In view of the great powers of resistance of anthrax spores in the environment, the question of contagion appears academic; and the occurrence of a large number of human cases in one locality might well be followed by serious epidemicity.

The anthrax bacillus grows abundantly in 24 hours on all ordinary media; it will grow at temperatures between 14 and 43 C. but does not form spores at the extremes, and is subject to attenuation of virulence at the higher temperatures. The rough variant is the virulent form. Spores develop in vitro only in the presence of oxygen; they appear readily in ordinary cultures, and are fully developed in 20-24 hours at 37 C. (74). The outstanding characteristic of the anthrax bacillus from the standpoint of bacterial warfare is the great resistance of its spores. They can survive and remain virulent for several years in the dark and in contact with air. Their longevity in soil is said to be at least 15 years (74), and damp low-lying marshy fields with abundant decomposing organic matter, once contaminated, may remain so indefinitely. The spores tolerate more than 100 C. when dry. Consequently the anthrax bacillus might qualify along with the clostridia for contamination of projectiles (see p. 19).

Natural infection in animals appears to be transmitted chiefly through the alimentary tract, indirectly by means of contaminated soil and pasturage as in France, and through imported fodder in Great Britain (276). Horse flies and mosquitoes may convey anthrax mechanically (188, 213, 276). In man, anthrax is distinctly an occupational disease, acquired by contact with infected animals or their products; and as mentioned above, infection may take place through the Cutaneous, alimentary or respiratory routes. In bacterial warfare the anthrax bacillus would probably be used in two general ways: to contaminate agents themselves intended to produce wounds, such as shrapnel or barbed wire; and by direct air transmission of spores. In the latter instance an accompanying respiratory irritant such as mustard gas might be used as a vehicle for the spores, although we know of no data on the resistance of anthrax spores in such a medium. It may be noted that certain other disease agents exert a definitely antagonistic action on the anthrax bacillus, notably *B. pyocyaneus* and staphylococci, perhaps also the typhoid bacillus and *E. coli*, and possibly vaccinia virus (71).

Vaccination of farm animals against anthrax, widely practiced since Pasteu time, is undoubtedly effective, although not free from objectionable featuie The total annual death rates of vaccinated animals have been 0.3 to 0.9 per cel per year as compared with death rates of 5 to 10 per cent before vaccinatie but the groups, differing in time and in conditions of exposure, are not con parable, and the precise degree of protection afforded by vaccination seems certain (74, 276). Vaccination has not been applied to man. If the antil bacillus were to be used as an instrument of warfare, the attacking forces wort certainly be vaccinated in advance, but it seems impossible to predict how col' plete would be the protection resulting. Moreover, vaccination carries ' own considerable risk, since living organisms are used with decreasing degrc of attenuation in successive injections. The death rates in vaccinated anirlin given above may be attributed at least in part to vaccination itself, not to we' tion the febrile and other reactions in animals following Pasteur vaccinatie' The method of serovaccination (250) is less toxic, but anaphylaxis may folle revaccination. It is possible that with present-day methods of chemical ft' tionation of antigens a completely innocuous but effective vaccine might developed.

Therapy with horse antiserum has been used widely in man, with appsl success in cutaneous anthrax. Present day practice appears to favor ner ' phenamine intravenously in addition to massive doses of serum (136). -I detection of anthrax following an attack should present no unusual difficulti assuming awareness of the possibilities. The characteristic organisms are - found by direct microscopic examination of stained smears of exudate fl'w, skin lesions or of sputum or other discharges. Identification by cultures, though they are easily obtained from the same sources, and in later sttig` from the blood, may be somewhat less reliable because the anthrax bacill closely resembles the ubiquitous environmental saprophytic spore-bea The anthrax bacillus, however, is distinctive in being non-motile, in liquef gelatin slowly, and in its pathogenicity for mice and guinea pigs. Post-more" diagnosis should include microscopic examination and culture of blood and gans, especially of the spleen. The Ascoli test, precipitation of boiled extrnl of anthrax blood or tissue by antiserum, is suitable for retrospective diap°" even after long periods.

As an agent of bacterial warfare, the anthrax bacillus could be expec(cel be as retroactive as epidemic agents of the first magnitude (such as plagilc influenza), chiefly because of the persistence of anthrax spores in the environro and of the great difficulties in effecting decontamination. Methods of dece tamination, as they are applied to wool, hides and other animal products, methods for disposal of infected animal carcasses, are discussed by ELIO' and Hewlett (74). It may be noted here that H2S has been found to be an off' tive germicide for both bacilli and spores, and it has been suggested (3) that e‘ casses be sprinkled with FeS powder and then moistened with dilute hydrochl" acid and covered with earth. Strong calcium hypochlorite has also been reco mended.

Bacillus (Pasteurella) Pestis

The bubonic form of plague has been discussed previously (page 23), and reasons have been given for considering it comparatively unsuitable for bacterial warfare. Pneumonic plague, on the other hand, despite its high retroactivity, may well be used as an agent of warfare. There is no reason to doubt that virulent plague bacilli could be disseminated by the air-borne route, and that under conditions which can be rather clearly defined, a devastating epidemic could result. Difficulties may be encountered less in provoking an epidemic than in finding means for controlling it once it had begun. Plague, like influenza and malaria, might be used to reduce a completely isolated stronghold such as an island naval or air base, with the view of rendering it useless to either side for an indefinite period.

Infectivity. In this respect the plague bacillus is superlative. Of the routes of infection that it may choose, only the cutaneous, the most common in nature (flea-bite) seems to engender any inflammatory resistance to the invader in the form of lymphadenitis—the bubo; yet even by this route a single plague bacillus can kill a guinea pig (7), and there seems to be no reason to believe that man is less susceptible. Six to 12 organisms, the smallest dose tried, killed 100 per cent of white mice in 5 to 7 days (251). Gay (101) states that infection of man with bubonic plague probably results from inoculation of very few organisms. There is little significant variation of human natural resistance to plague infection (211).

Casualty effectiveness. The incubation period of all types of plague apparently varies from 2 to 10 days (101). In Madagascan experience, it was characteristically 5 days, rarely 6 or 7, never more than 9, so that a 10-day quarantine was considered safe (105). In the less severe bubonic form, death may occur 3 to 5 days after onset, and the case mortality is never less than 50 per cent, and may be 95' per cent. The septicemic and pneumonic forms are fatal invariably or with very rare exceptions (216,267).

Availability. The plague bacillus grows readily on all ordinary media, and undergoes attenuation of virulence only after prolonged artificial cultivation. It will grow over a wide range of temperature, but virulence is best maintained at 25-30 C. rather than at 37 C. (255, 203, 13, 251). Sokhey (251) has presented detailed data on mass cultivation of virulent strains used for the preparation of the killed vaccine widely employed in India.

Resistance. Among the wealth of data available on this score the most significant appear to be those that indicate prolonged resistance and maintenance of virulence of plague bacilli frozen, or frozen and desiccated, in sputum, exudates or tissues under natural conditions. Strong (267) states that the bacilli retain their virulence for several weeks or even months under such conditions; "when such sputum becomes frozen and pulverized, it may be blown about and remain infective for considerably longer periods of time than when in the form of moist droplets." Francis (94) found that sealed cultures remained alive and virulent at 10 C. for at least 9 years, and also for prolonged periods in guinea pig spleen in pure glycerin at —15 C. Cultures transferred each month on agar slants and held at laboratory temperature (always less than 26 C.) remained virulent

for from 3 to more than 8 years (255); cultures grown on 5 per cent rabbit blon, agar slants at 26-29 C. for 4 days, then sealed and stored at about 4 C., remaine, virulent at least 3 years (251). On the other hand, transfers at weekly interva at 37 C. for a year impaired virulence (203), as did serial subculture every hours on rabbit blood agar with continuous incubation at 37 C. (13). Surviv , and maintenance of virulence in the flea for periods of several months has alF, been reported by several authors (216, 178, 72, 73).

Attempts to preserve plague bacilli by deliberate freezing and desiccatio do not seem to have been made, but, in accordance with the principles developc- by Heller (128), it seems probable that preservation in the presence of the ingrt dients of a nutrient medium would be successful by the lyophile method (847

Plague bacilli, on the other hand, are easily destroyed by sunlight, heat are disinfectants. Exposure to 55 C. may destroy them in 5 minutes,. although '- effective minimal conditions for preparation of the killed virulent vaccin, given as 55 C. for 15 minutes (253). In sputum, the organisms are destroyc by 10 per cent phenol in 5 minutes, and by 5 per cent mercuric chloride in 2 minutes (101). *B. pestle* apparently does not persist in the environment fo' long periods in warm weather, except in the bodies of infected rats and nor..

Means of transmission. Plague infection can apparently take place by an. of the routes made use of by other disease agents. Infection may also be estal: lished by contact with the mucous membranes of mouth or throat (267' Infection through the skin can occur independently of fleas, and infection h: the respiratory tract has been repeatedly demonstrated in animals (174, 268,6T and undoubtedly occurs also in man. Except for pneumonic plague, in whit: "enormous numbers of uniformly highly virulent microorganisms" are lona+ in the sputum (267), the organisms are not easily discharged into the environ meat, so that biting vectors are essential intermediaries under natural conditioin

Epidemicity. It is unnecessary here to review at length the usual mantle of origin of a pneumonic epidemic through secondary pneumonia in but oi plague. The facts that seem most germane to the present discussion .:1 (a) that the organism responsible for pneumonic plague is in no way differer_ from that which causes the bubonic form; and (b) that once primary pn, eumonii plague has been established through the mechanism mentioned, it spreads with. out the aid of reservoir, vector, or any other secondary agency. As far a bacterial warfare is concerned, contamination of water in cold but not freeziii weather seems conceivable; but the primary route appears clearly to be via tin air. Strong (267) states that,

> Anyone . . . who is willing to take the risk can easily demonstrate that by spraying per cultures of highly virulent plague bacilli, free from any other organism . . . there produced in guinea pigs, monkeys or tarbagans who breathe the atmosphere containing plague bacillus, outbreaks of typical primaryplague pneumonia as observed in b0rio" beings.

The text-books describe the mechanism of spread of pneumonic plague terms of "droplet infection." In view of what has been said on page 19,

seems unnecessary to labor the point here that this conception is inadequate. The known resistance of the plague bacillus to environmental influences in cold weather makes it eminently probable if not certain that pneumonic plague is capable of transmission at a distance in both space and time, without intermediaries. It is important, however, to consider the climatic conditions under which such transmission occurs. Small outbreaks of pneumonic plague have been reported from tropical regions (220, 269), but the severest epidemics have occurred in cold climates, as for example in Manchuria (267).

According to Strong (267) the pulmonary disease occurs especially in cold weather and under conditions of crowding and lack of sanitation. The Madagascan workers have reported that pneumonic plague is favored by temperatures below 59 F. (216). The low humidity associated with cold climates is also generally suggested as a favorable influence. It may be noted that bubonic plague seems on the contrary to require high humidity for epidemicity, as well as a temperature below about 80 F. (24). The latter conditions are apparently those required for survival of the rat flea; whereas the transmission of pneumonic plague depends on survival of the plague bacillus free in the environment. The dissemination of virulent plague bacilli via the air from low-flying planes in a heavy menstruum like a smoke screen, which would filter through openings into habitations, or, if feasible, by means of projectiles, could be expected to induce an epidemic whose severity would be directly proportional to the density of the population attacked, under appropriate conditions of temperature and humidity. Even though dissipation of the bacterial "smoke" in the open air might make the initial attack-rate low, only a few cases in any compact army camp or other concentration of men might well be the focus of a devastating epidemic.

Specific immunization. Since vaccination against plague has been authorized by the United States Army, this subject need not be reviewed here in detail. The living avirulent vaccines of Otten (203), Girard (105) and Robic (216) seem to be more effective than the killed vaccine used in India, although as Strong (267) points out, full sterilization is advisable where large numbers are to be vaccinated. The living vaccine, however, appears to have a remarkable record of safety. Only 2 reactions, both transient, have been recorded in 1,500,000 vaccinations with a living strain (105). At best, vaccination against plague reduces but does not abolish plague morbidity; and the case mortality is evidently unaffected.

Therapy. Both serum (267) and sulfonamides (65) have been used with some success in treatment of bubonic plague. Good results have been reported with sulfapyridine and sulfathiazole in animals (65, 106, 230, 252). Except for scattered case reports, the only field study of chemotherapy reported thus far (289a) is a series of 237 cases in an Indian epidemic treated with either serum, sulfapyridine or sulfathiazole. As compared with a 52 per cent mortality in untreated controls, the treated groups had mortalities of 28, 24, and 15 per cent respectively. The overall reduction in mortality is considered to be statistically valid, but not the differences between the three treated groups. The authors

state that even in severe septicemic cases mortality was reduced from abOu per cent to about 40 per cent by sulfathiazole. It is of special interest that six cases of primary pneumonic plague seen in the epidemic, two given intr.*: venous iodides as controls died in 3 days; of four treated with about 4 grams pc: day of sulfathiazole, two died on the third day, one on the fourth, and one c' the eleventh day. The blood in these cases became sterile and remained The authors believed that the dosage may have been too small.

Detection. Despite the fact that buboes, the most important single diagnodd feature of plague, would probably be absent in an induced epidemic of prieL:, monic plague, rapid identification of the disease would probably not be diffiet [17] The organisms are easily isolated from the sputum, or, particularly in septiceri [-7], plague, from the blood. For post-mortem diagnosis comparatively fresh in fected organ suspension, preferably spleen, should be injected subcutaneovvt: or intraperitoneally into guinea pigs; if the material is putrid, it should be rulir · into the shaved abdomen of a guinea pig or on to its nasal mucosa (276).

Retroactivity and protection. It is possible that vaccination, combined %vita prophylactic and therapeutic use of a suitable sulfonamide compound, migiC be used to control a plague epidemic, or to prevent its retroactive infection cm troops entering an epidemic area. It may be, that bacteria-proof masks,coill augment such protection. In the absence of adequate experimental data c- [7], of results of suitable field trials, however, it seems rash to suggest that any sue T. combination of measures would be effective.

Common Cold Virus

The high infectivity of cold virus and the universal susceptibility to it sugge ·' it as an agent. However, the virus is so ubiquitous as to render artificial dit' semination of doubtful value. The agent has been cultivated on the chic ·] embryo and found to be infective for human volunteers (62, 190).

Influenza Virus

Among the air-borne virus diseases, influenza, alone or in conjunction ''vit bacterial and other viral agents, may serve as an effective weapon in bacteri warfare. Influenza ranks with plague as an agent of great potential retroactis H ity. Considerable attenuation has been noted in cultivated strains of the Several investigators have produced only mild symptoms in human vo10 [1]- teers after intranasal inoculatimi (61, 248); yet the possibility of initiating severe epidemic of influenza cannot be excluded.

Infectivity. The morbidity rate of pandemic influenza is very high. In ill --- 1889 pandemic, an average figure was 345 per 1000; in the 1918 pandemic ',- corresponding figure was 280 (190). The attack-rate of interpandemic is said to be much lower (285). On artificial inoculation of ferret-grown influeliz" virus by the intranasal route, Smorodintseff and his collaborators (248) reperVQ · that 20 per cent of 72 human volunteers showed clinical symptoms of n1: [1],[7] influenza. Similar observations had previously been made by Dochez (i[1]: with egg-grown influenza virus. Their results led the Soviet workers to conch)

that ferret- and mouse-grown strains were relatively harmless for man. The virus disappeared from the throat within 24-48 hours and did not seem to activate potentially pathogenic bacteria such as pneumococci, streptococci or *H. influenzae.* It may be noted that these experiments were conducted immediately after an epidemic in Leningrad, and that most of the subjects were found to have a considerable titre of antibodies in their serum. Chambers (36) has recently obtained results indicating much higher infectivity for man. This work was done at a time when no influenza had occurred in the region for a year. Chambers was testing the effectiveness of a vaccine for human influenza and subjected groups of vaccinated and non-vaccinated individuals to the virus by inhalation. In the non-vaccinated group 60 per cent developed *severe* influenza requiring hospitalization.

Availability. At least two serologically different strains are available in addition to swine influenza virus. They can all be readily transmitted to ferrets and mice (247, 131) and have been successfully propagated for as many as 86 generations on the chorio-allantoic membrane of the egg, as well as in tissue culture (226, 147, 196). Both animal and culture strains have shown considerable attenuation of virulence for man (61, 248).

Resistance. Virus dried on cotton, serge, impregnated house dust and other materials still retains considerable activity (69). The virus has been lyophilized and found to be infective for ferrets after 15 months (131).

Means of transmission. Influenza virus is one of the agents which have been shown capable of transmission by the air-borne route by methods such as those discussed on page 20. Wells and Henle (296) have shown that influenza A virus suspended in air will produce typical infections in mice and ferrets on inhalation. Compound infections with virus and type I pneumococci increased the severity of the disease and its mortality rate. Similar studies (2) have also shown transmission by coarse and fine droplets; and nasal infection of ferrets with group C streptococci was found to be possible only in conjunction with influenza A virus. There is no reason to doubt that the air-borne route of transmission operates in man.

Epidemicity. Diseases in the influenza group, all of which are considered to be of virus etiology, vary in epidemicity over a wide range, from sporadic cases or small outbreaks to world-wide pandemics which rank with the Black Plague of the 14th Century among the great epidemic scourges of mankind. The causative agent of the last great pandemic of influenza in 1918 was not isolated at the time; and whether and how it may have differed from strains of virus isolated subsequently has not been determined (190). The potential epidemicity of an outbreak of influenza initiated in bacterial warfare, if such an epidemic could be produced at all, is consequently unpredictable.

The serological relationship established by Shope (236) between swine influenza and the human influenza pandemic of 1918 may be of significance. Shope demonstrated the dual etiology of the disease in swine as due to virus in combination with *H. influenzae suis.* If the swine virus is actually an adapted pandemic human strain, the possibility that it could be readapted to man is of

fundamental importance from the standpoint of bacterial warfare. It ma` he that either swine or human influenza virus strains might be more effective ht-man if combined with *H. influenzae* than if used alone. Smorodintseff (240 has shown that human volunteers exposed to *H. influenzae* by inhalation developed an illness within 4 to 6 hours in all of 110 exposed subjects. The disea:41, however, was mild, and lasted for only one day. It was distinctly differe0 from influenza.

Specific immunization. Many attempts have been made to immunize 1111/vv. subjects against influenza, with disappointing results. More recently, the Pro - duction of only mild disease by intranasal instillation of mouse- and ferteti grown virus, with concomitant formation of neutralizing antibodies, led to suggestion (248) that inhalation immunization with attenuated virus may prove practicable. This possibility remains to be explored adequately.

Therapy. No specific therapy against influenza is available.

Detection. The clinical features of influenza are well known, but diagno,,is may nevertheless be difficult. The atypical pictures which may result from ar - tificially induced epidemics, especially if the virus is used in combination wide other agents, may further complicate the problem. The use of neutralizatiun and complement-fixation tests, however, should facilitate disclosure of nature of the virus within a short period.

Retroactivity. The method of dissemination of influenza virus in warfare which is most likely to be effective would be the spreading in dust of large gum,- titles of virus together with *H. influenzae,* pneumococci, streptococci and possil '1;- meningococci over troops and thickly inhabitated areas by aircraft. As suq, - gested above, both the eventuality of an epidemic following such dissemination, and the likelihood or degree of epidemic spread that might follow are not predicta - ble on the basis of the available data. It may be said, indeed, that the suitabilit of influenza virus as an agent of bacterial warfare, and the military uses to which it might be put, are matters which can be determined satisfactorily only further investigation.

The Viruses of Measles and Mumps

The properties of these two viruses make them almost ideal choices as agent' of bacterial warfare. Mumps virus has not yet been cultivated and is therei or - unavailable, but the close parallelism of the two diseases warrants their con - sideration together. Although both diseases occur characteristically in child-hood, they have assumed great importance in military cantonments during war-time. During World War I mumps stood third on the list of diseases an ,1 casualty producer, with measles following in the same range. Both dis,r,sc' are highly epidemic and it is believed that infection follows exposure of sus-ceptible individuals in about 95 cases out of 100. Both have a low morta litti rate except for respiratory complications. Since recovery is accompanied 1, 'Y durable immunity, and since many soldiers have had either or both diseases 1,1 childhood, the use of selected immune troops for entering contaminated territ "rr may be capable of solving the problem of retroactivity.

Infectivity. Both diseases are highly infective and may occur in epidemic form especially in young adults in areas free from previous contact with the viruses. Military establishments, which bring together large numbers of individuals from different localities, are likely to bring many susceptibles into contact with the agents. Two great peaks in the attack-rate of mumps occurred during the Civil War and World War I. In 1917-19 there were 239,490 cases of mumps in the U. S. Army and 168,519 in 1918 alone (299).

Casualty effectiveness. In measles the incubation period is 10-11 days, followed by listlessness, drowsiness, and catarrhal conjuctivitis; fever, occasionally relapsing in character, may reach 102° or even 104°F. The disease lasts 7 to 10 days unless respiratory complications occur (71). The most common complication, responsible for most measles deaths, is a streptococcal broncho-pneumonia.

The incubation period of mumps is somewhat longer than that of measles, oy followed by involvement of the parotid glands and sometimes of the testes or ovaries. Meningoencephalitis occurs. There is considerable immobilization, with headache, fever, and posterior pharyngitis. The malaise and discomfort disappear in 7 to 10 days. Mortality is very low, especially in adults, but may be increased by complications such as nephritis (285).

Availability. The virus of measles can now be grown on the chorio-allantoic membrane of the chick embryo (297a). It has been cultivated in several laboratories and there is little reason to doubt that the required quantities can be made available (226). The culture virus is infective for monkeys. The virus of mumps has not been grown in tissue or egg culture. The disease has, however, been maintained in monkeys for several generations (142, 80), and Johnson and Goodpasture (142) were then able to transmit it back to human volunteers. Mumps virus may be isolated from saliva and blood during the first 6 days of infection. Only successful cultivation is needed in order to make this virus available as a military agent of wide potential usefulness.

Resistance. The data on resistance of measles virus are meagre. It is stated that the virus resists freezing for 25 hours, room temperature for 24 hours, and 50 per cent glycerin for 3 months, and that it is destroyed at 55 C. in 15 minutes (285). The virus of mumps is resistant to drying, freezing and glycerolation. (142).

Means of transmission. Both viruses are probably transmitted chiefly by the air-borne route. Experimental data on this point are lacking, but the notorious capacity of both diseases to spread rapidly and widely through children's wards or army camps strongly suggests this mechanism.

Epidemicity. Both measles and mumps are "endemic-epidemic" in urban areas. Measles is virtually universal among city children. It is stated (299) that 80 to 90 per cent of urban populations have mumps before the age of 16, whereas only 15 to 20 per cent of rural populations have the disease. At Camp Upton in 1917, of 1059 cases of mumps, 85 per cent were in men originally from rural areas. Mumps was most prevalent among southern troops, and was usually acquired within, the first three months of service.

Specific immunization. Although second attacks of both diseases are known, in the vast majority of instances recovery confers permanent immunity. No artificial methods of immunization are used in either disease.

Therapy. In both diseases convalescent serum has been used, in measles V produce an attenuated form of the disease, and in mumps as a prophylactie. In measles, care must be taken to permit adequate exposure to infection; other wise durable immunity is not established. Convalescent serum in mumps should be given within one week of exposure (299); the passive immunity produced lasts about two weeks. Convalescent serum for use in mumps is usually obtained 10-14 days after defervescence.

Detection. Neither disease offers any especial problems in diagnosis to the clinician.

Retroactivity. The degree of immunity following recovery from both measles and mumps is sufficiently high so that the use of selected troops, who had recovered from the disease, to enter the attacked area, may alone solve the probleif of retroactivity.

Pathogenic Neisseria

Previous writers on bacterial warfare have in general dismissed the pathogenic Neisseria because of difficulties in cultivation, maintenance of virulence, and low capacity for survival in air. Recent improved methods for maintenance of virulent cultures, and the lyophile processes for drying bacteria, have over these difficulties, but the suitability of these organisms for bacterial warfare remains questionable. The gonococcus is probably not practicable becamc of its low infectivity by non-venereal routes, which would be the only practicable ones in warfare. The infectivity of the meningococcus likewise appears to beI very low, the morbidity rate being only 0.01 to 0.3 per cent even in epidemic periods (276). Epidemics are usually associated with wartime conditions, overcrowding, fatigue and lowered resistance, and have been considered a seriole problem among armies. Since the outbreak of the present war there has beef an unprecedented increase in the disease in England-12,500 cases in 1940— le all probability because of congestion and overcrowding particularly as a result of bombing.

Carriers play a very important role in the transmission of meningocosettl meningitis. Before and during epidemics a large proportion of the populatiel are found to carry the organism (22). The normal carrier rate among troop` in World War I was 2 to 4 per cent, but during pre-epidemic periods it reached 20-30 per cent. Soon after the level passed 20 per cent cases began to appear and the carrier rate rose concomitantly to as high as 88 per cent (276). Ever' so, as indicated above, only relatively few cases of frank disease appeared (60) A bacterial attack with this organism would thus probably have as its purpos(' the production of a carrier rate high enough so that cases would appear. Larg' quantities of virulent lyophilized cultures could be obtained for this purpcee (21, 150, 60). Except for the psychological effect of inciting the characteristic

fear of this disease, which might be accomplished by even a small outbreak, it seems doubtful that this agent, by itself, could serve a useful military purpose. The meningococcus may find more important military applications as a combined or secondary organism with other air-borne agents.

Psittacosis Virus

The properties of psittacosis virus suggest that it may be one of the most useful agents of bacterial warfare. It is an air-borne agent of high infectivity for man. Large amounts of virus are readily obtainable, and retroactivity may be controllable by vaccination.

Infectivity. McCoy (168) states that within 2 months after work on psittacosis was begun at the Hygienic Laboratory, 11 cases developed among 54 persons working in the building in which the virus was being studied. No infections appeared in adjoining buildings. Two of 3 persons who handled infected parrots and parakeets developed the disease, as did one of two persons who had been studying cultures. None of the other 8 cases had had anything to do with the psittacosis work. McCoy states: "this so far as we know is the first example of the infection occurring through the medium of contaminated environment without contact with infected birds. This occurrence suggests that the infectiveness for man is of a very high order." Armstrong (4) noted 16 laboratory infections and 2 deaths. Hull (136) recorded 38 laboratory infections up to 1929-30. •Aside from such laboratory infections, psittacosis has always been associated with contact with infected birds. Cases occur at all ages, but children appear to be relatively resistant.

Casualty effectiveness. The incubation period is given as 6 to 15 days by Armstrong (4) and as 9 to 10 days by McCoy (168). Armstrong's study of 169 cases indicated that the onset may be rather sudden, or may follow a few days of vague indisposition. The disease is characterized by chills, headache and fever of 100-102°F., rising to 103-105°, with irregular remissions during the second week. Focal lung lesions with physical signs, and an unproductive cough, usually develop. There may be chest pains, anorexia, constipation and abdominal distention. A leukopenia develops by about the 20th day. Delirium is usually associated with high temperature. Fever may terminate after about 8 days, or may continue for three weeks or more. Relapses occur fairly often, during or after three weeks of normal temperature. Death usually occurs from the 7th to the 15th day, but may occur later, and is usually due to an apparently specific pneumonia. Out of 169 cases in the epidemic of 1929-30, 33 deaths are recorded (4). Deaths are most common in persons over 30. Convalescence is very slow.

Availability. The virus of psittacosis is readily cultivable both in tissue culture and on the ehorio-allantoic membrane of the chick embryo (226). Burnet and Rountree (31) note that repeated egg passage did not appear to affect virulence for eggs or for mice. These authors carried out as many as 14 passages on hen or duck eggs.

Resistance. The virus remains active in glycerin at pH 7.4 for at least 66

days at 5 C. Desiccated bird spleens remained virulent for 277 days aa l,, same temperature. Certain strains increase in mouse virulence by rep eated passage, and dilutions of 10⁻" have proved effective in some instances (181). An Australian strain of psittacosis virus is much less virulent than the Europ ean or American strains (179).

Means of transmission. Data such as those of McCoy (168) strongly su ggest that psittacosis virus is an air-borne agent. Meyer, Eddie and Stevens (1 81) believe that aerial convection is the important factor in transmission. Monk ey although insusceptible by the subcutaneous route, develop disease simila r to psittacosis in man after intratracheal inoculation (181). Birds acquire infection by the enteric route (179). It is noted below that parenteral administr at ion of active virus in man may result in immunity without producing disease.

Epidemicity. Outbreaks of psittacosis in man have occurred predomin antly in relation to contact with infected birds, but 23 instances of man-tos man transmission had been recorded up to 1939 (179). Nurses have frequently become infected from patients. Meyer (179) cites an instance of a quad ruple man-to-man infection chain: bird dealer—physician—intern—nurse 1 —nurse 2. Virus has been demonstrated in human sputum from the 5th to the 37tk d ay after onset, but appearance of virus is irregular in individual patients. The disease spreads mainly in winter, although cases have been reported in mid summer; and multiple cases in one household are common (181). Recovered human cases may carry the virus (179). The data leave no doubt that ma n-t a-man transmission occurs; yet such transmission does not seem to be the rule in nature. The degree of epidemicity that might follow a successful attack with psittacosis virus is yet to be determined.

Specific immunization. Rivers and Schwentker (215) have devised a method of vaccination against psittacosis by intramuscular injection of active virus. Immunized persons developed as high a titre of neutralizing antibodies a s ac-companies recovery from the disease. Such parenteral administration of the virus did not produce psittacosis.

Detection. Diagnosis of psittacosis is said to be difficult except in relation to history of contact with birds. This fact might cause considerable dela y in diagnosis after initial use of the agent in bacterial warfare. The observation, of Meyer, Eddie and. Stevens (181) that Java sparrows are especially susceptible, and "may serve as excellent sentinels for the detection of the presence and the dissemination of the virus in a room or pen in which parakeets with latent psittacosis are held" should be of great lialue in rapid identification of the agent. Complement-fixation tests are also useful in detection of possible carriers and in diagnosis (182).

Therapy. Armstrong (4) notes foal- cases in which convalescent serum was used, all of which were associated with relapses after 3 to 4 weeks of normal temperature. No extensive data on serum therapy are available.

Retroactivity. The possibility exists that persistent contamination of a region may result after attack with psittacosis virus, because of the production of human carriers and by the formation of reservoirs of virus in local birds. Immediate retroactivity to troops entering an attacked area may be controllable through the use of the vaccination method of Rivers and Schwentker (215).

Presumptive air-borne infections.

Bacillus (Malleomyces, etc.) Mallei

Glanders in both horses and man has become so uncommon in recent years in the United States and in Western Europe that virulent cultures of the glanders bacillus may not be readily available. The disease is still prevalent, however, in parts of Asia, Africa and Russia (137). Since there is little current literature on this subject, much of what follows is derived from text-books.

Infectivity. Glanders is a disease of horses and other equine animals, and less commonly of man. The organism is highly infective for certain laboratory animals, particularly the guinea pig, which can be infected through the intact skin and by inhalation of pulverized cultures as well as by the usual routes (6). °\` Babes (6) found that guinea pigs infected by inhalation developed disease of the lungs, whereas rabbits infected by this route or by inoculation on the normal conjunctiva or nasal mucous membrane died of septicemia without local lesions. Although natural infection of man has never been common and is now extremely rare, many laboratory infections are said to have occurred despite ordinary precautions (136, 276). Topley and Wilson (276) consider the organism one of the most dangerous of all bacteria to laboratory workers, perhaps second only to the bacillus of tularemia. There is some reason to believe (see availability) that pure cultures may be more dangerous to man than infected exudates or discharges.

Glanders does not occur at all in cattle, and swine appear to have little or no susceptibility. In addition to equidae, which are most frequently affected, the disease also affects sheep, goats, cats, dogs and menagerie animals, and perhaps pigeons (143); and field mice as well as guinea pigs and rabbits can be infected experimentally.

Casualty effectiveness. Two types of the disease occur in both horses and man, an acute form with primary 'respiratory symptoms which is fatal in 1 to 6 weeks (136), and a chronic form ("farcy" in horses) with skin and bone lesions of tuberculoid Character, which may continue for years, leading to recovery or death from acute exacerbation. The chronic form is the more common in horses, but the reverse seems to be true of man. Mortality in the acute form is given as 60 per cent of cases (136). Gaiger (99), who described the course of chronic glanders in himself, had an incubation period apparently of less than a week. In the fatal case described recently by Herold and Erikson (129) the incubation period was evidently about 2 weeks. The disease is extremely painful and incapacitating.

Availability. Bacillus mallei can be cultivated without difficulty on ordinary media, preferably in the presence of small amounts of glycerin. It requires 2 or 3 days' incubation at 37 C., but will grow at any temperature from 22 to 44 C. It is said to be indifferent to moderate variations in pH; a potato-glycerol

veal agar at pH 6.4 has been recommended (205). Freshly isolated cultures. are highly virulent. Some strains lose virulence in culture; however, according to Nicolls (195), other strains do not become entirely avirulent after m o nths or even years of cultivation on artificial media.

Resistance. B. mallei is easily killed by moist heat (55 C. for 10 minntes) and by disinfectants. Cultures rarely survive more than 6 weeks, and infected pus or discharges, when dried, usually become sterile in a few days (276). pure cultures may be more resistant to desiccation than bacilli in nasal secretions or in diseased animals (143), and this circumstance may help to explain the comparative rarity of glanders in man from contact with diseased horses, and the frequency of laboratory infections. Cultures dried on threads are said t o live 3 or 4 weeks (276), and the organisms may survive 25 days in distilled water (205). Calcium hypochlorite with 2 parts per million of free chlorine kills the organisms in 30 minutes (276), and with 1 part per thousand in 1 or 2 minutes: strong solutions of sodium carbonate are also useful for disinfecting stables and utensils (205).

Transmission. Glanders in man is largely occupational, associated with contact with horses. Infection is believed to occur chiefly through skin abra - sions or injuries, although it is also said to have caused primary localization in the nasal mucosa (276), and the intact conjunctiva (145). Infection has also been thought to occur by ingestion, but this seems an uncommon route, since meat from glandered animals has been eaten without inducing infection (143). The early experiments of Babes (6), previously cited, seem to be the only ones which suggest the air-borne route. The possibility that air-borne infection znaY occur naturally in man is mentioned but not emphasized in the text-books. Whether or not this means of transmission occurs naturally, the chance that it might be used effectively in warfare is a serious one, and points to the need for further animal experimentation on its practicability.

Epidemicily. Glanders has evidently been transmitted from man to man, but extremely rarely. Washerwomen are said to have been infected from the clothes of a patient (205). Robins (217) found only 15 cases out of 156 to be directly associated with other human cases. Considering the rarity of glanders in man, the severely incapacitating nature of the disease, and the apparel) th' feeble resistance of bacilli in sputum or pus, a low degree of epidemieity does not seem surprising despite high potential infectivity. Potential epidemieiV under warfare conditions can nevertheless not be excluded. Glanders bacilli' occur in the nasal secretions of patients, in the pus from nodules, and sometime , in the urine, saliva and milk (205). If the organism is capable of air-hems transmission the concurrence of several cases under conditions of crowding in cold weather such as are usually favorable to the spread of respiratory infection , might possibly induce a severe epidemic.

The disease is evidently rapidly epizootic among horses, although perliap ; less so than Brucella infection in cattle, since slaughter seems to have been more effective in controlling glanders (143). Glanders used to be especially prev - alent in the large studs of horses owned by the Municipal Omnibus Companic , in London (276); once the infection had been introduced, it spread rapidly throughout the stud. Symptomless infection may occur in horses, as indicated by the mallein test, and apparently healthy horses may spread the disease through public drinking troughs and in blacksmith shops (205).

French writers on bacterial warfare (see especially Duffour, 1937) have suggested that Germany intended, and perhaps attempted, to use glanders bacilli on the western front in 1916. A reference to cattle as victims in a quotation from a supposedly incriminating document, however, suggests doubt as to the authenticity of the story.

Specific immunization. Recovery from glanders confers no permanent immunity, and attempts at artificial active immunization with killed or attenuated cultures or with mallein have not provided convincing results (305).

Therapy. No generally accepted procedure is available. Slaughter of infected horses appears to be the main recourse, and has been used successfully. Recovery has been reported in man after use of autogenous glanders vaccines (23, 48); and useful results with serum therapy have been reported in a small number of human cases (291, 200).

Detection. Because of its rarity in man, and particularly if cases in man were to occur without the usual occupational history, diagnosis might present great difficulty. Suspicion of the disease can be verified fairly easily, however, by bacteriological methods. The organism is readily isolated from nasal secretions or nodular exudate on glycerol agar and provisionally identified by the Straus reaction: intraperitoneal inoculation of a male guinea pig is followed in 2 or 3 days by orchitis. This reaction is also given by the bacillus of melioidosis, which, however, can be distinguished by its motility, growing more rapidly on agar at 37 C (24 hours as compared with 48 or more for *mallei),* and producing a characteristically wrinkled or rugose colony. Brucella strains may also give a Straus reaction, but in this instance the infection is rarely progressive or fatal in the guinea pig, whereas both mallei and whitmori are likely to induce severe general symptoms and death of the animal in two weeks or less. Brucella infection in man can also be distinguished by the absence of the respiratory or skin lesions characteristic of glanders, and by the agglutination and other antigen-antibody tests; since Brucella and *B. mallei* are antigenically unrelated (302). Specific agglutination and the mallein test are useful in human glanders only in the chronic form.

Retroactivity. From the indications given under transmission and epidemicity, it is evident that studies on animals of the glanders bacillus under conditions of simulated warfare are required before any prediction as to either its effectiveness or its potential retroactivity can be made. The high infectivity, severe casualty effectiveness and easy availability of the organism suggest that such experiments may procure valuable information.

Bacillus Whilmori (Malleomyces Pseudomallei)

The bacillus of a rare glanders-like disease of rats and man, melioidosis, which appears to be limited to the Malay Archipelago and neighboring parts of Indo-